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(54) Title: COMPOSITIONS FOR TREATMENT OF CHRONIC INFLAMMATORY DISEASES		
(57) Abstract <p>This invention defines novel compositions which can provide a basis for clinical treatment of several chronic inflammatory diseases, said diseases including varieties of arthritis, ileitis, colitis and other inflammatory disorders, as well as trauma resulting from ischemia and subsequent reperfusion. Increased lipid peroxidation is a common to the etiology of all of the clinical disorders addressed herein. Such increased lipid peroxidation generates carbonyl substances which are cytotoxic and additionally serve to perpetuate and disseminate the inflammatory process. This invention involves use of orally administered amine derivatives of benzoic acid as carbonyl trapping agents. These primary therapeutic agents act by chemically binding to and sequestering the aldehyde and/or ketone products of lipid peroxidation. p-Aminobenzoic acid (or PABA) is an example of the primary agent of the present invention. PABA has a small molecular weight, is water soluble, has a primary amine group which should react with carbonyl-containing metabolites under physiological conditions and is tolerated by the body in relatively high dosages and for extended periods. The method of the present invention includes administration of a composition comprising (1) a therapeutically effective amount of at least one carbonyl sequestering primary therapeutic agent, (2) optionally one or more co-agent such as, for example, an anti-oxidant free radical trapping substance, and (3) at least one medicament recognized as effective to treat said chronic inflammatory disease, so as to produce an additive or synergistic physiological effect of an anti-inflammatory nature.</p>		

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COMPOSITIONS FOR TREATMENT OF CHRONIC INFLAMMATORY DISEASES

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to the clinical treatment of chronic inflammatory diseases, including chronic gingivitis; chronic periodontitis; chronic autoimmune gastritis; ileitis; inflammatory bowel disease, including colitis; interstitial cystitis; psoriasis; arthritis; tendinitis; carpal tunnel syndrome and other cumulative trauma disorders; lupus erythematosus; pneumoconiosis; chronic obstructive pulmonary disease; inflammatory myopathies; inflammatory neuropathies, including Alzheimer's disease, myasthenia gravis and multiple sclerosis; epilepsy; as well as lessening of inflammatory site edema, and treatment of post-event ischemia and reperfusion symptomology resulting from acute central nervous system trauma, stroke, kidney ischemia or myocardial infarction.

2. Description of Prior Art

The logic and potential value, even *synergistic* value, of using two or more therapeutic agents in combination for treatment of chronic inflammatory diseases has been recognized previously (Calhoun and coworkers, 1992; Hirschelmann and coworkers, 1991; Brooks and Schwarzer (1991); Wright and coworkers, 1977).

The present disclosure describes the inventive concept of using the therapeutic technology of US Patent Application 07/906,909 in combination with pharmaceutical agents having some medicinal value for treatment of the disease entities noted above. The inventive concept embodied in my earlier US Patent Application 07/906,909 filed 30 June 1992 is the use of compositions consisting of a primary agent which sequesters carbonyl products in combination with co-agents that have known anti-oxidant properties. The primary agents of the present invention, such as p-aminobenzoic acid (PABA), contain

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a primary amine group, so as to enable reaction with carbonyl groups of disease-related substances. No pharmacological treatment of comprehensive effectiveness is currently available for any of the chronic inflammatory disorders discussed herein. However, a variety of pharmaceutical agents have been described which may offer at least some degree of symptomatic relief from the clinical effects of these diseases.

Clinical use of the drug sulfasalazine (SAZ) represents a well documented example of the use of a benzoic acid derivative as a trapping agent for the hydroxyl radical and other free radicals in the treatment of a chronic inflammatory disease. In the colon SAZ undergoes reductive cleavage to liberate 5-aminosalicylic acid (5-amino-2-hydroxybenzoic acid, or 5-ASA), which is the therapeutically active agent. Ahnfelt-Ronne and coworkers (1990) presented research findings which document the use of SAZ for successful treatment of chronic inflammatory bowel disease (CIBD), also known as ulcerative colitis. SAZ is also recognized for use in treatment of ileitis (Budavari and coworkers, 1989, pg. 1412). Ahnfelt-Ronne (1990) compared their in vivo 5-ASA metabolic products to products observed after in vitro hydroxylation of 5-ASA by the Fenton reaction and tentatively identified 5-ASA metabolites as being hydroxylated derivatives. They never attempted to look for evidence of in vivo trapping of carbonyl products. Under the brand name *Asacol* and the generic name mesalamine, 5-amino-2-hydroxybenzoic acid in delayed-release tablets has also been marketed in the United States for use in treatment of CIBD (Dowd and coworkers, 1993, pgs. 1868-1869). Dull and coworkers (1987, pg. 2469) used mass spectrometry to definitively identify two of the several hydroxylation/oxidative deamination products which result from in vitro incubation of 5-ASA with activated human mononuclear cells. They identified these products as gentisic acid (2,5-dihydroxybenzoic acid) and salicylic acid (2-hydroxybenzoic acid), while five other 5-ASA metabolic products remained unidentified (pg. 2470).

Ahnfelt-Ronne and colleagues, Dull and coworkers, and earlier investigators never recognized the possibility of using a therapeutic agent to scavenge carbonyl products of

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inflammation. Hence they never recognized the possibility of intentionally using a composition consisting of a primary agent which sequesters carbonyl products in combination with co-agents that have known anti-oxidant properties.

Further distinctions should be noted between the invention disclosed in US Patent Application 07/906,909 and previously recognized clinical use of SAZ. SAZ releases sulfapyridine, a somewhat toxic substance, into the body (Peppercorn, 1984, pgs. 377-379 and 383), while the invention of US Patent Application 07/906,909 does not. In addition, use of sulfasalazine depends on intestinal bacteria for activation of the drug, while the primary agents of the present invention do not. Besides use in treatment of CIBD, SAZ has been recognized, at least at the experimental level, for treatment of ileitis, radiation bowel disease, scleroderma, dermatitis herpetiformis and rheumatoid arthritis (Peppercorn, 1984, pgs. 380-381).

Other examples of amine drugs recognized as having anti-inflammatory properties include para-substituted N-benzene-sulfonyl derivatives of anthrilic acid (Borne and coworkers, 1974), 4-amino benzoic acid anilides (Thiele, 1971; Deutsche Gold- und Silber-Scheideanstalt vorm. Roessler, 1972), tinoridine (Shimada and Yasuda, 1979) and benzothiazolinone derivatives (Takashima and coworkers, 1972). The chemical structures of these agents lie beyond those of the primary agents of the present invention. They are not presently recognized as carbonyl sequestering therapeutic agents. They have not been used in multiple ingredient compositions analogous to those of the present invention.

Several drug products containing PABA have been marketed for human use in the United States. However, it is believed that none have been proposed as effective for the treatments claimed herein. Potassium p-aminobenzoate has been marketed as Potaba (R) in the pure form as an antifibrotic, that is, skin softening, agent (Drug Information for the Health Care Professional, 8th ed., 1988, pgs. 111-113). As such it has been recognized for treatment of Peyronie's disease; diffuse systemic sclerosis; morphea and linear scleroderma; and dermatomyositis. For such purposes, Potaba is taken orally in

average doses of 12 gm/day for up to two years, although human use of 15 - 20 gm/day is recognized. As an ingredient in analgesic tablets, PABA has been marketed for domestic human use (300 mg/tablet) in *Pabirin* (R) buffered tablets (with aspirin), in *Pabalate* (R) tablets (with sodium salicylate) and in *Pabalate-SF* (R) tablets (with potassium salicylate), as described in Physicians' Desk Reference (Huff and coworkers, 1980, pgs. 849, with aspirin and 1430, with salicylates). Five percent PABA in a cream base has also been marketed as a sunscreen product (Physicians' Desk Reference, Huff and coworkers, 1980, pg. 849).

In its summary on systemic use of potassium p-aminobenzoate the Drug Information for the Health Care Professional text (8th ed., 1988, pg. 111) presented the following statement regarding recognized pharmacology (reproduced herein its entirety):

Mechanism of action: The mechanism by which aminobenzoate potassium exerts its antifibrotic effect is not known. It has been postulated that fibrosis results from an imbalance of serotonin and monoamine oxidase (MAO) mechanisms at the tissue level. Fibrosis is believed to occur when an excessive serotonin effect is sustained over a period of time. This could be the result of too much serotonin or too little MAO activity. Aminobenzoate potassium increases oxygen utilization at the tissue level. It has been suggested that this increased oxygen utilization could enhance the degradation of serotonin by enhancing MAO activity or other activities that decrease the tissue concentration of serotonin.

In its summary on systemic use of potassium p-aminobenzoate the Physician's Desk Reference (Dowd and coworkers, 1993, pg. 1103) presented the following statement (reproduced herein its entirety):

INDICATIONS

Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications as follows:

'Possibly' effective: Potassium aminobenzoate is possi-

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bly effective in the treatment of scleroderma, dermatomyositis, morphea, linear scleroderma, pemphigus, and Peyronie's disease.

Final classification of the less-than-effective indications requires further investigation.

ADVANTAGES

POTABA offers a means of treatment of serious and often chronic entities involving fibrosis and nonsuppurative inflammation.

PHARMACOLOGY

P-Aminobenzoate is considered a member of the vitamin B complex. Small amounts are found in cereal, eggs, milk and meats. Detectable amounts are normally present in human blood, spinal fluid, urine, and sweat. PABA is a component of several biologically important systems, and it participates in a number of fundamental biological processes. It has been suggested that the antifibrosis action of POTABA is due to its mediation of increased oxygen uptake at the tissue level. Fibrosis is believed to occur from either too much serotonin or too little monoamine oxidase activity over a period of time. Monoamine oxidase requires an adequate supply of oxygen to function properly. By increasing oxygen supply at the tissue level POTABA may enhance MAO activity and prevent or bring about regression of fibrosis.

This inventor sees no relationship of such comments to the present invention. In particular, the comments noted above clearly do not recognize the potential use of PABA and derivatives thereof as carbonyl trapping agents, that is, as agents which may generally inhibit chronic inflammatory disorders by virtue of their ability to chemically bind to and sequester aldehyde and ketone products of lipid peroxidation which result from and contribute to the continuation of chronic inflammatory disorders. In addition, prior art information has not anticipated or disclosed the particular compositions set forth in the present disclosure. Hence the clinical applications of PABA and derivatives thereof claimed in the present invention are regarded by the inventor as new

and novel.

Certain amine agents have recognized anti-oxidant properties. These include *N,N'*-di-(*sec*-butyl)-*p*-phenylenediamine (Scott, 1965, pg. 120), aniline (Scott, 1965, pg. 125), aniline *N*-substituted agents (Scott, 1965, pg. 125), *N,N'*-diphenyl-*p*-phenylenediamine (Swingle and coworkers, 1985, pg. 112) and ethoxyquin (Swingle and coworkers, 1985, pg. 112). In the present invention focus is placed on primary amine agents, as such agents are known to covalently react with carbonyl agents to yield Schiff base-type products (Feeney and coworkers, 1975, pg. 141). By contrast, *N*-substitution with hydrocarbon functional groups tends to increase amine anti-oxidant activity (Scott, 1965, pgs. 125 and 148). These are two distinct chemical phenomena. The anti-oxidant property of amines depends on their ability to act as electron donors to alkoxy or alkylperoxy radicals (Scott, 1965; pgs. 127, 145 and 158). The carbonyl trapping property of amines depends on their ability to form Schiff base-type addition products.

Zarafonetis (1953) has reported some success in treatment of rheumatoid arthritis by use of potassium *p*-aminobenzoate in combination with acetylsalicylic acid and cortisone. In this report Zarafonetis also described some success in clinical treatment of dermatomyositis and scleroderma by use of potassium *p*-aminobenzoate alone, and referred to earlier work on these disorders and other clinically related syndromes, including forms of lupus erythematosus.

Yet Zarafonetis based his logic for diversifying clinical studies on PABA or its potassium salt solely on similarities of clinical symptoms, comparisons among clinical syndromes which feature some common symptomology (Zarafonetis, 1953, pgs. 667-668; Zarafonetis, 1964, pgs. 550 and 560; Priestley and Brown, 1979, pg. 161; Zarafonetis and coworkers, 1988, pg. 194). Zarafonetis never stated an understanding or recognized that PABA has the physiological potential of serving as an aldehyde chemical trapping agent (Zarafonetis, 1953, pg. 671). Hence, he never recognized its potential to sequester aldehyde products resulting from increased lipid peroxidation secondary to site-specific inflammation. In failing to recognize this principle, Zarafonetis failed to recognize the potential full

scope of clinical applications of PABA.

Failing to recognize the potential of synergistic anti-oxidant co-agents, the procedures of Zarafonetis for treatment of scleroderma, rheumatoid arthritis and dermatomyositis relied on use of high PABA dosages (12-18 gm/day; see Zarafonetis, 1953, pg. 666). In principle, it is the understanding of the present inventor that the clinical prognosis of any disease which features increased lipid peroxidation as part of its etiology may be improved by clinical application of the inventive concept embodied herein.

Zarafonetis (1953) also referred to an earlier study which used a combination of p-aminobenzoic acid and α -tocopherol to treat scleroderma. Gougerot and Hewitt (1951) described the logic of their scleroderma treatment protocol as follows:

This observation is to be added to the file of the treatment of sclerodermas. Zarafonetis and his collaborators have already published 5 cases of sclerodermas improved by para-aminobenzoic acid, and in the same therapeutic series Shaffer and his collaborators treated a generalized scleroderma with para-aminobenzoic acid with improvement. In a study of a completely different nature, vitamin E (α -tocopherol) was used by Klemperer, etc. and in France by Bazex (Lyon, July 1949). This is why we have associated the two therapies because of their effect on diseases of collagen.

As such, they perceived their clinical treatment strategy to address the status of collagen, with no discussion of possible physiological mechanisms. Compared to the invention embodied herein, Gougerot and Hewitt: (1) failed to recognize that either of their therapeutic agents may interfere with the inflammatory cascade, (2) failed to recognize that primary amine and amine-related derivatives of benzoic acid, as a class, may bind to and sequester aldehydes which result from the inflammatory process, (3) failed to understand that the combination of a water soluble aldehyde-trapping primary amine agent and a lipophilic anti-oxidant agent may have clinical application to the treatment of a broad spectrum of chronic inflammatory diseases, and (4) failed to disclose the unique

positions of the present invention.

In 1967 Mel'nikova and Ryzhova presented the results of a clinical trial wherein PABA was used to treat post-event trauma in experimental myocardial infarction, as studied in rabbits and dogs. They reported a coronary vasodilator effect of PABA based on their understanding of the drug's antihistamine property. They recognized no anti-inflammatory property of PABA and did not understand their findings within such a context.

Subsequent work by Kurdin (1978) has presented evidence of increased lipid peroxidation in the process of myocardial infarction. Actually, the association of increased levels of reactive oxygen species with ischemic myocardial dysfunction, with resulting lipid peroxidation is now well recognized (Dowling and coworkers, 1990, pg. 465). Viewing the reports of Mel'nikova and Ryzhova, Kurdin, and Dowling and coworkers within the context of the present invention, the inventor proposes that, to some degree, the beneficial effects of PABA in the Mel'nikova and Ryzhova study reflected an anti-inflammatory property of PABA unrecognized by the investigators, and that such a beneficial effect may be optimized by use of the multi-component compositions as defined in the present invention. Seekamp and Ward (1993), using a rodent hind limb ligature model of ischemia/reperfusion, have presented some data which demonstrated the value of anti-oxidant pre-treatment of animals with catalase, superoxide dismutase, dimethylsulfoxide, dimethylthiourea or deferoxamine. As itemized by Entman and coworkers (1991), a variety of therapeutic strategies has been proposed for treatment of ischemia/reperfusion trauma, yet none of these proposed strategies include the present invention.

The phenomenon of hypoxia/reperfusion injury is now understood to be an important aspect of several traumatic disease states, including coronary infarction, ischemic acute renal failure and cerebral ischemia (Dowling and coworkers, 1990, pg. 466). Hence, the present invention has significant clinical value in the post-event treatment of ischemia and reperfusion injury subsequent to myocardial infarction, acute kidney failure, and acute central nervous system trauma and

stroke. In light of the common physiological relationship of hypoxia/reperfusion conditions and chronic inflammatory diseases, both of which include tissue damage caused by lipid peroxidation and subsequent liberation of carbonyl substances, hypoxia/reperfusion conditions are considered to be varieties of chronic inflammatory diseases within the context of this invention. Likewise, as the etiology of Alzheimer's disease is believed to have an autoimmune component, and use of drugs such as deferoxamine (McGeer and Rogers, 1992, pg. 448; Halliwell, 1991, pg. 593) and indomethacin (Schnabel, 1993) has been previously noted in this regard, this disease also will be considered to be a variety of chronic inflammatory disease within the context of this invention.

Broad spectrum clinical use of anti-inflammatory vitamin compositions which feature PABA as a primary agent, and the methodological reasoning for doing so, has not been previously recognized or described prior to submission of US Patent Application 07/906,909. p-Aminobenzoic acid is not presently recognized as a nonsteroidal anti-inflammatory drug (NSAID). Hence, for example, it is not included in the lists of such drugs published in (a) the Merck Index, (Budavari and coworkers, 1989, pgs. THER-15 to THER-16), (b) Scientific American (Weissmann, 1991, pg. 86), (c) Understanding Arthritis (Kushner, 1984, pgs. 52-53) and (d) the American Journal of Medicine (Houston, 1991). Likewise, PABA is not recognized as being a "slow acting" anti-inflammatory agent (Understanding Arthritis, Kushner, 1984, pgs. 55-57).

Both PABA and D-penicillamine are primary amine agents which also function as anti-oxidant free radical trapping agents. Yet as anti-oxidant agents PABA and D-penicillamine are presently regarded as being of secondary, nominal value, due either to weak anti-oxidant properties or toxic side effects, respectively. Thus their use as anti-inflammatory agents has been quite limited. Their potential value for trapping the aldehyde products of inflammation-related lipid peroxidation has never been recognized. Hence the formulation of a new composition, such as one having PABA as its primary agent, optionally having known anti-oxidant free radical scavenging chemicals as co-agents, lacking vitamin C in excess

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of its RDA and additionally including a recognized medicament as defined herein, has never been previously described, and the potential for clinical use of such a novel composition in treatment of chronic inflammatory diseases has never been recognized.

Further distinctions should be made between the present invention and previously recognized use of penicillamine, one of the "slow-acting" anti-inflammatory drugs mentioned in Understanding Arthritis (Kushner, 1984), a publication of the Arthritis Foundation. The primary amine agents described in the present invention are all derivatives of aminobenzoic acid or aminophenylacetic acid, which should facilitate their safe elimination from the body by normal kidney filtration. D-Penicillamine is not a derivative of aminobenzoic acid or aminophenylacetic acid. In addition, D-penicillamine has a reduced sulfhydryl group, unlike any of the primary agents claimed herein.

The invention embodied herein constitutes an alternative slow-acting anti-inflammatory protocol which is believed to be inherently safer for the patient and to act via a mechanism not previously recognized or described. PABA is not among the antimalarial drugs discussed by Kushner (1984, pg. 57), nor is it among the antimalarial drugs listed in the Merck Index (Budavari and coworkers, 1989, pg. THER-16).

Many NSAID's are known to commonly induce side effects which include gastrointestinal damage, liver toxicity and kidney toxicity (Brune and Beck, 1991; Kraag, 1985). Most of these drugs antagonize the actions of many antihypertensive drugs (Houston, 1991). A variety of less common side effects of these drugs have also been reported (O'Brien and Bagby, 1985). Use of the present invention in combination with such previously recognized medicaments permits the effective use of such drugs at lower dosage levels, serves to permit use, in at least some cases, of previously known medicaments for more extended periods of time and serves to supplement the overall clinical benefit to patients. Recognized nonsteroidal anti-inflammatory drugs include aminoarylcarboxylic acid derivatives, arylacetic acid derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid derivatives,

pyrazoles, pyrazolones, salicylic acid derivatives, thiazine-carboxamides, ϵ -acetamidocaproic acid, *S*-adenosylmethionine, amixetrine, bendazac, benzydamine, bucolome, difenpiramide, ditazol, emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, perisoxal, pifoxime and proquazone. Within the context of the present invention, the following additional drugs should also be regarded as nonsteroidal anti-inflammatory drugs: phenidone; ketoconazole; disodium azodisalicylate (a dimer of mesalamine); diazo sulfanilamide ethylene polymer of 5-aminosalicylate; cyclophosphamide; 6-(2,4-difluorophenoxy)-5-methylsulfonylamino-1-indanone; ditazol; droxicam; azapropazone; etoclofene; prenazone; 7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2*H*-1-benzopyran-2-carboxylic acid; *N*-acetylcysteine; *S*-carboxymethylcysteine; naphthyramide; flavonoids such as sideritoflavone, cirsilinol, hypolaetin-8-glucoside, hypolaetin, oroxindin, quercetagenin-7-glucoside, gossypin, hibifolin, gossypetin and leucocyanidol; tepoxalin, sodium 2-[4-(2-oxocyclopentylmethyl)phenyl]propionate dihydrate, 1-[(4-chlorophenyl)methyl]-2-methyl-5-(quinolinylmethoxy)-1*H*-indole-3-acetic acid, DL-2-(4-hexyloxyphenyl)glycine octyl ester, DL-2-[4-(5,5-dimethylhexyloxy)phenyl]glycine octyl ester; and 6-methoxy-2-naphthylacetic acid. Likewise, within the context of the present invention various gastrointestinal anti-inflammatory drugs, antimalarial drugs and antiarthritic/antirheumatic drugs as disclosed in the Merck Index, 11th edition (Budavari and coworkers, 1989) are regarded as nonsteroidal anti-inflammatory drugs.

Glucocorticoid drugs are well known. A more complete listing of specific examples of such drugs, and of the various forms in which these therapeutic agents may be administered, can be found in various well known reference works such as, for example, the Merck Index, 11th edition (Budavari and coworkers, 1989).

Henceforth reference to sanguinarine will include reference to hydrated and salt derivatives thereof, such as for example sanguinarine monohydrate, sanguinarine chloride and sanguinarine chloride dihydrate. Co-agent use of all forms of amino-glycoside, amphenicol, ansamycin, β -lactam, lincosamide,

macrolide, polypeptide and ¹²tetracycline antibiotics are claimed within the scope of the present invention, as well as use of cycloserine, mupirocin and tuberlin. The various forms of these antibiotics are known to those skilled in the art and information regarding them can be found in various reference works, for example, the Merck Index, 11th edition (Budavari and coworkers, 1989). Information regarding nonsteroidal anti-inflammatory drugs recognized for use by local administration or oral administration is known to those skilled in the art and may be found in reference works such as the Physicians' Desk Reference, 47th edition (Dowd and coworkers, 1993).

Henceforth reference to prednisone will include reference to its pharmaceutically acceptable ester derivatives thereof, such as for example prednisone 21-acetate. Henceforth reference to prednisolone will include reference to its pharmaceutically acceptable ester and salt derivatives thereof, such as for example prednisolone 21-diethylaminoacetate, prednisolone 21-stearoylglycolate, prednisolone 21-tert-butylacetate, prednisolone 21-trimethylacetate, prednisolone 21-acetate, prednisolone sodium succinate, prednisolone sodium 21-m-sulfo-benzoate, and prednisolone sodium phosphate. Henceforth reference to cortisone will include reference to its pharmaceutically acceptable ester and salt derivatives thereof, such as for example cortisone 21-acetate, 21- β -cyclopentanepropionate cortisone, cortisone phosphate, cortisone monosodium phosphate, cortisone disodium phosphate and cortisone phosphate dimethyl ester. Henceforth reference to hydrocortisone will include reference to its pharmaceutically acceptable ester and salt derivatives thereof, such as for example hydrocortisone 21-acetate, hydrocortisone 21-bendazac, hydrocortisone 17-butyrate, hydrocortisone 17-valerate, hydrocortisone tebutate, hydrocortisone 21-sodium succinate, hydrocortisone disodium phosphate and its progenitor, hydrocortisone phosphate. Henceforth reference to methylprednisolone will include reference to its pharmaceutically acceptable ester and salt derivatives thereof, such as for example methylprednisolone 21-acetate, methylprednisolone sodium 21-succinate and methylprednisolone disodium 21-phosphate. Henceforth reference to triamcinolone will include reference to its pharmaceutically ac-

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ceptable ester and ether derivatives thereof, such as for example triamcinolone 16 α ,21-diacetate, triamcinolone acetone, triamcinolone acetone 21-acetate, triamcinolone acetone di-sodium 21-phosphate, triamcinolone acetone 21-hemisuccinate, triamcinolone benetonide and triamcinolone hexacetone. Henceforth reference to betamethasone will include reference to its pharmaceutically acceptable ester and salt derivatives thereof, such as for example betamethasone 21-acetate, betamethasone 21-adamantoate, betamethasone 17-benzoate, betamethasone 17,21-dipropionate, betamethasone 17-valerate, betamethasone 17,21-divalerate, betamethasone disodium phosphate and betamethasone monosodium phosphate. Henceforth reference to dexamethasone will include reference to its pharmaceutically acceptable ester and salt derivatives thereof, such as for example dexamethasone 21-acetate, dexamethasone 21-(3,3-dimethylbutyrate), dexamethasone tetrahydrophthalate, dexamethasone 21-diethylaminoacetate, dexamethasone 21-isonicotinate, dexamethasone 17,21-dipropionate, dexamethasone 21-palmitate, dexamethasone 21-phosphate and dexamethasone disodium 21-phosphate. Additional forms of glucocorticoids are known to those skilled in the art and information regarding them can be found in various reference works, for example, the Merck Index, 11th edition (Budavari and coworkers, 1989).

The various forms of anticholinergic drugs such as scopolamine, trihexyphenidyl, benztropine mesylate, procyclidine, biperiden, ethopropazine, propantheline and oxybutynin are known to those skilled in the art and information regarding them can be found in various reference works, for example, the Merck Index, 11th edition (Budavari and coworkers, 1989).

Salicylic acid is recognized as being both an antiseptic and a keratolytic agent (Budavari and coworkers, 1989).

Based on its clinical and structural similarities to D-penicillamine, 5-thiopyridoxine may be regarded within the context of the present invention as an example of a non-steroidal anti-inflammatory drug which may be useful in the treatment of rheumatoid arthritis.

Immunomodulator substances as defined within the context of the present invention include, for example, those noted in

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Budavari and coworkers (1989, pg. THER-25), as well as leflunomide, diaveridine, apocynin, 1-p-chlorobenzyl-2-dimethylaminomethylcyclohexen-1,2, (Z)-3-[4-(acetyloxy)-5-ethyl-3-methoxy-1-naphthalenyl]-2-methyl-2-propenoic acid, diacetylsplenopentin, solubilized chicken type II collagen, dapsone, capsaicin, (10-methoxy-4H-benzo[4,5]-cyclohepta-[1,2-b]-thiophene-4-yliden)acetic acid, eicosapentaenoic acid, lobenzarit, tiopronin (also known as N-2-mercaptopropionylglycine), tenidap, diacetylrhein, interferons, copolymer-1 and 2,6-Diamino-N-[[1-(1-oxotridecyl)-2-piperidinyl]methyl]hexanamide, tilomisolone, indoxole, bimetopyrol, flumizole, scalaradial, kojic acid, misoprostol, 1-[3-(naphth-2-ylmethoxy)phenyl]-1-(thiazol-2-yl)propyl methyl ether, and 4-(2-chlorophenyl)-2-[2-(4-isobutylphenyl)-ethyl]-6,9-dimethyl-6H-thieno[3,2-f][1,2,4]triazolo-[4,3a][1,4]-diazepine.

Hydroxychloroquine, quinacrine, chloroquine and amodiaquine are examples of antimalarial drugs in the present invention. A more complete listing of specific examples of this group, and of the various forms in which the respective therapeutic agents may be administered, can be found in various well known reference works such as, for example, the Merck Index, 11th edition (Budavari and coworkers, 1989).

Within the context of the present invention, diazepam and lorazepam are regarded as anxiolytic drugs of the benzodiazepine variety. A more complete listing of specific examples of benzodiazepine anxiolytic drugs, and of the various forms in which the respective therapeutic agents may be administered, can be found in various well known reference works such as, for example, the Merck Index, 11th edition (Budavari and coworkers, 1989). Carbamazepine, clonazepam, ethosuximide, lamotrigine, phenobarbital, phenytoin, primidone, valproic acid, vigabatrin and zonisamide are anticonvulsant drugs. Likewise, as phenytoin-polyvinylpyrrolidone coprecipitate releases phenytoin in vivo, this drug may also be regarded within the context of this invention as an example of an anticonvulsant drug. As acetazolamide is regarded as an alternative to ethosuximide, clonazepam or valproate for treatment of petit mal seizures, this drug and its sodium salt derivative may also be regarded as examples of anticonvulsant

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drugs within the context of the present invention. A more complete listing of specific examples of anti-convulsant drugs, and of the various forms in which the respective therapeutic agents may be administered, can be found in various well known reference works such as, for example, the Merck Index, 11th edition (Budavari and coworkers, 1989).

Captopril and ketanserin are examples of antihypertensive drugs. A more complete listing of specific examples of antihypertensive drugs which may be useful in the treatment of Alzheimer's disease as defined herein, and of the various forms in which the respective therapeutic agents may be administered, can be found in various well known reference works such as, for example, the Merck Index, 11th edition (Budavari and coworkers, 1989).

Henceforth reference to ephedrine will include reference to derivatives thereof, such as, for example, ephedrine hydrochloride, ephedrine sulfate and ephedrine tannate. Pyridostigmine and neostigmine are cholinergic drugs. A more complete listing of specific examples of cholinergic drugs, and of the various forms in which the respective therapeutic agents may be administered, can be found in various well known reference works such as, for example, the Merck Index, 11th edition (Budavari and coworkers, 1989). Atropine and propantheline are anticholinergic drugs. A more complete listing of specific examples of anticholinergic drugs, and of the various forms in which the respective therapeutic agents may be administered, can be found in various well known reference works such as, for example, the Merck Index, 11th edition (Budavari and coworkers, 1989).

Baclofen and tizanidine are skeletal muscle relaxant drugs. A more complete listing of specific examples of skeletal muscle relaxant drugs, and of the various forms in which the respective therapeutic agents may be administered, can be found in various well known reference works such as, for example, the Merck Index, 11th edition (Budavari and coworkers, 1989). Amitriptyline and imipramine are tricyclic anti-depressant drugs. A more complete listing of specific examples of tricyclic antidepressant drugs, and of the various forms in which the respective therapeutic agents may be

administered, can be found in various well known reference works such as, for example, the Merck Index, 11th edition (Budavari and coworkers, 1989).

Cyproheptadine is an example of an antihistaminic drug of the tricyclic variety, and clemastine and setastine are examples of anti-histaminic drugs of the aminoalkyl ether variety. A more complete listing of specific examples of antihistaminic drugs, and of the various forms in which the respective therapeutic agents may be administered, can be found in various well known reference works such as, for example, the Merck Index, 11th edition (Budavari and coworkers, 1989).

A more complete listing of specific examples of anticoagulant drugs beyond those disclosed below, and of the various forms in which the respective therapeutic agents may be administered, can be found in various well known reference works such as, for example, the Merck Index, 11th edition (Budavari and coworkers, 1989). Tissue plasminogen activator and streptokinase are thrombolytic drugs. Likewise, a more complete listing of specific examples of thrombolytic drugs than those disclosed below, and of the various forms in which the respective therapeutic agents may be administered, can be found in various well known reference works such as, for example, the Merck Index, 11th edition (Budavari and coworkers, 1989).

Aminophylline is a member of the xanthine derivative class of bronchodilators. Isoproterenol is a member of the ephedrine class of bronchodilators. A more complete listing of specific examples of bronchodilator drugs, and of the various forms in which the respective therapeutic agents may be administered, can be found in various well known reference works such as, for example, the Merck Index, 11th edition (Budavari and coworkers, 1989). Within the context of the present invention, aminophylline, isoproterenol and methohexital sodium may be regarded as examples of antithrombotic drugs.

The various forms of β -adrenergic blockers are known to those skilled in the art and information regarding them can be found in various reference works, for example, the Merck Index, 11th edition (Budavari and coworkers, 1989). The various forms of calcium channel blockers are known to those skilled in the art and information regarding them can be found

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in various reference works, for example, the Merck Index, 11th edition (Budavari and coworkers, 1989). Glyceryl trinitrate, isosorbide dinitrate and isosorbide 5-mononitrate are examples of antianginal drugs. A more complete listing of specific examples of antianginal drugs, and of the various forms in which the respective therapeutic agents may be administered, can be found in various well known reference works such as, for example, the Merck Index, 11th edition (Budavari and coworkers, 1989).

SUMMARY OF THE INVENTION

These and other objects of this invention are achieved by providing a novel method and compositions for clinical treatment of chronic inflammatory diseases. This invention involves use of orally administered amine derivatives of benzoic acid and partially or fully saturated analogs as carbonyl trapping agents. These primary therapeutic agents act by chemically binding to and sequestering the aldehyde and/or ketone products of lipid peroxidation. Increased levels of lipid peroxidation have been repeatedly demonstrated as a part of the "inflammatory cascade" process which underlies the secondary etiology of chronic inflammatory diseases. p-Aminobenzoic acid (or PABA) is an example of the primary absorbable pharmacological agent of the present invention. PABA has a small molecular weight, is water soluble, has a primary amine group which should react with carbonyl-containing metabolites under physiological conditions and is tolerated by the body in relatively high dosages and for extended periods. The present invention is directed to the use of carbonyl sequestering agents administered in oral dosages, optionally in combination with co-agents consisting of clinically effective anti-oxidant free radical trapping agents and agents related thereto, and in combination with medicaments so as to produce a physiological effect of an anti-inflammatory nature. Optional co-agents of the present invention include anti-oxidants (e.g., alpha-tocopherol), suspending reagents (e.g., carboxymethyl cellulose), other vitamins, vitamin-related agents, chemical conjugating agents which may facilitate kidney drug elimination (e.g., glycine), and orally administered non-absorbable

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polyamine or polyamine-related agents (e.g., chitosan or cholestyramine). Particular additional medicaments useful in the present invention are disclosed herein.

OBJECTS OF THE INVENTION

Accordingly, it is a general object of this invention to treat chronic inflammatory diseases by use of compositions comprising carbonyl trapping agents optionally but preferably in combination with known anti-oxidant free radical trapping co-agents, factors related to anti-oxidant free radical trapping co-agents, and additionally with known medicaments, so as to create compositions with additive or synergistic physiological therapeutic characteristics and so as to overcome the disadvantages of the prior art.

It is a further object of this invention to facilitate the effectiveness of this anti-inflammatory procedure by use of orally consumed carbonyl trapping polymeric co-agents which are of a nonabsorbable nature, so as to bind and sequester carbonyl chemical agents which are present in food, thus preventing such toxic agents from being absorbed into the body.

In particular, it is an object of the present invention to use absorbable amine primary agents; optional nonabsorbable amine polymeric co-agents, co-agents which inhibit lipid peroxidation, vitamin co-agents which may be inadvertently depleted, co-agent metabolites such as glycine which may be depleted within the body, sulfhydryl co-agents as defined herein, co-agents which may facilitate glutathione activity; and various additional known medicament co-agents which have been shown to or may contribute to the alleviation of symptomology of the diseases addressed herein, thus improving upon the prior art.

It is an object of the present invention to provide compositions that may be used to provide increased clinical value in the treatment of disease symptomology for disorders featuring lipid peroxidation and resultant formation of toxic carbonyl compounds, including: chronic gingivitis; chronic periodontitis; chronic autoimmune gastritis; ileitis; inflammatory bowel disease, including colitis; interstitial cystitis; psoriasis; arthritis; tendinitis; carpal tunnel syndrome

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and other cumulative trauma disorders; lupus erythematosus; pneumoconiosis; chronic obstructive pulmonary disease; inflammatory myopathies; inflammatory neuropathies, including Alzheimer's disease, myasthenia gravis and multiple sclerosis; epilepsy; as well as lessening of inflammatory site edema, and treatment of post-event ischemia and reperfusion symptomology resulting from acute central nervous system trauma, stroke, kidney ischemia or myocardial infarction.

It is another object of the present invention that in so far as the therapeutic procedures described herein may serve to delay the necessity of initiating the use of known medicaments or to decrease the dosages of known medicaments required to achieve beneficial effects, the period of prior art drug therapeutic value may be extended and detrimental clinical side effects resulting from use of known medicaments may be decreased, so that overall patient treatment may be improved.

It is a further object of this invention that the absorbable amine and amine-related substances and derivatives thereof described herein when used in combination with specified co-agents may be clinically applied to treat veterinary disorders comparable to at least some of those human disorders described above.

These and other objects of the present invention will be apparent from the following detailed description.

DETAILED STATEMENT OF THE INVENTION

It is known that aldehyde chemical metabolites, which contain carbonyl functional groups, are generated during the process of chronic inflammation. These aldehyde products result from pathologically increased lipid peroxidation, which may be initiated by a variety of activated oxygen chemical species such as the hydroxyl radical, HO \cdot (Halliwell and Gutteridge, 1985, pp. 119-120). The reactive cascade of free radical propagation \rightarrow lipid peroxidation \rightarrow aldehyde formation and other subsequent effects of inflammation is well documented in the prior art (Halliwell and Gutteridge, 1985, pp. 102-103). The secondary carbonyl products of lipid peroxidation include saturated and unsaturated aldehydes, dialdehydes, epoxyaldehydes, lactones, furans, ketones and oxo

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acids (Merry and coworkers, 1991, pg. 362S). As reactive oxygen species are generated in vivo during states of limited oxygen availability, followed by reperfusion, a similar series of reactions takes place at sites of hypoxia/reperfusion injury (Demopoulos and coworkers, 1980; Dowling and coworkers, 1990, pg. 465). Aldehyde products of this reactive cascade are known to react with amino acids to form Schiff bases, and to react with free amino groups of proteins, nucleic acids and phospholipids (Hatherill and coworkers, 1991, pg. 352).

Prior to submission of my above-cited US patent application, the method concept of using carbonyl-trapping agents such as primary amine or amine-related derivatives of benzoic acid to treat chronic inflammatory diseases was not recognized or disclosed. Thus, the application of this principle in conjunction with use of known anti-oxidant free radical trapping agents to produce new and novel compositions which have improved, synergistic therapeutic properties also was not recognized.

The invention embodied herein is based on use of a composition of a primary amine derivative as defined herein as a primary agent for chemically binding to and sequestering aldehyde products of inflammation site lipid peroxidation together with a medicament, and optionally their use in combination with anti-oxidant free radical trapping co-agents. This unique, multiple-level approach to interference with certain steps in the inflammatory cascade has not been previously recognized by other research investigators. This is, in fact, the first anti-inflammatory agent invention which addresses the issue of aldehyde formation at inflammation sites. As aldehydes are highly reactive molecules capable of reacting with proteins, lipids and nucleic acids (Jellum and coworkers, 1973, pg. 200; Carden and coworkers, 1986; Halliwell and Gutteridge, 1985, pg. 123), their increased formation at inflammation sites can be a significant contributing factor in the evolution of the clinical pathology of inflammatory disorders.

The results of several published research studies suggest that dysfunctional lipid peroxidation may be a contributing factor in the etiology of a variety of chronic inflammatory diseases, such as rheumatoid arthritis (Jasin, 1993; Merry and

coworkers, 1991; Panetta and ²¹coworkers, 1991; Rowley and coworkers, 1984), multiple sclerosis (Hunter and coworkers, 1985), silicosis (Katsnelson and coworkers, 1989, pg. 318), Duchenne muscular dystrophy (Kar and Pearson, 1979; Jackson and coworkers, 1984), colitis (Tamai and coworkers, 1992) and chronic inflammatory bowel disease (Ahnfelt-Ronne and coworkers, 1990). As exposure to asbestos fibers can stimulate lipid peroxidation (Halliwell and Gutteridge, 1985, pg. 152) and a chronic inflammatory response (Rom and coworkers, 1991, pg. 415), asbestosis should also be included in this category. Published evidence has also documented the generation of high free radical concentrations at the inflamed site of experimental foot pad edema (Dowling and coworkers, 1990, pg. 464), the ability of carbonyl compounds resulting from lipid peroxidation to induce foot edema in the rat (Benedetti and coworkers, 1980), and that formaldehyde is known to be an inflammatory and edematogenic agent (Wheeler-Aceto and Cowan, 1991). In addition, a role for reactive oxygen radicals has been proposed for numerous other disorders, including inflammatory vasculitis, emphysema, mineral dust pneumoconiosis and autoimmune nephrotic syndromes (Halliwell and Grootveld, 1987, pg. 10).

Ischemia/reperfusion damage to various tissues appears to occur by a common mechanism, involving generation of free radicals and lipid peroxidation (Fleckenstein and coworkers, 1991). Increased lipid peroxidation has also been demonstrated in acute central nervous system trauma (Hall, 1987, pgs. 421 and 424; Demopoulos and coworkers, 1980, pgs. 97 and 112; Kontos and coworkers, 1981, pg. 2329), as a result of stroke (Zivin and Choi, 1991, pg. 61), subsequent to myocardial infarction (Kurdin, 1978) and in an experimental model of myocardial ischemia (Siminiak and Wysocki, 1992). Increased lipid peroxidation under such circumstances appears to be initiated by extravasation of blood, as iron-containing substances such as hematin catalytically accelerate lipid autoxidation (Demopoulos and coworkers, 1980, pgs. 97 and 115). Status epilepticus has also been linked to increased intracellular concentrations of free radicals, with subsequent lipid peroxidation (Del Maestro, 1980, pg. 163).

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Recent studies have also disclosed the possibility that the etiology of Alzheimer's disease may include an autoimmune component, thus establishing a conceptual link to disorders such as rheumatoid arthritis and systemic lupus erythematosus (Saso and coworkers, 1993). Evidence of an etiological role for lipid peroxidation in Alzheimer's disease has been disclosed (Ceballos and coworkers, 1990).

It is further understood that oral use of nonabsorbable carbonyl trapping agents may serve to prevent absorption of dietary aldehydes and ketones from the alimentary tract into the body, thus complementing the intended therapeutic results.

(i) Mechanism of Action of Primary Agents

For the most part, these pharmacological reactions are based on the ability of the primary amine compounds of the present invention to react with aldehyde functional groups of potentially toxic agents, yielding covalently bound Schiff base products. Several examples of chemically analogous reactions, presented within other contexts, have been publicly presented (Holdren and Hixon, 1946; Sawicki and coworkers, 1963; Chio and Tappel, 1969; Dunlop and Peters, 1953, pgs. 353, 371 and 373). These model chemical systems are directly analogous to the mechanism of drug action which is the basis of the present invention.

Additionally, self-polymerization of o-aminobenzaldehyde has been described. In the 1994 edition of the Sigma Chemical Company catalog of biochemical reagents the following statement appears on page 90 of its listing: "o-AMINO BENZALDEHYDE Unstable! [store at] -20°C Polymerizes rapidly when exposed to room temperature. May yield slightly hazy solution in ethanol due to presence of a small amount of polymer. Shipped in dry ice." This information directly indicates that a primary amino group covalently linked to a benzene ring possesses sufficient reactivity for significant reaction with aldehyde functional groups at room temperature. It is apparent that no form of activation of the amino group is required and that a Schiff base product forms readily.

Comments by Feeney and coworkers (1975, pg. 141) provide an appropriate summary of this prior art:

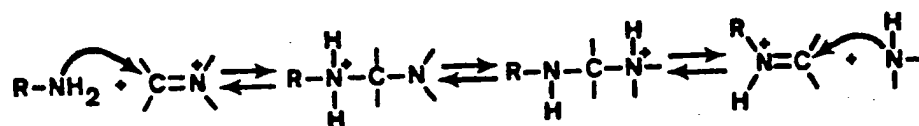
A wide variety of substances with -NH₂ groups con-

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dense with carbonyl compounds... This condensation of primary amines with aldehydes and ketones to give imines was first discovered by Schiff (1900). The overall equilibrium greatly favors hydrolysis in aqueous solution for aliphatic aldehydes. With aromatic aldehydes, the equilibrium is shifted in favor of Schiff base formation. It is important to note that increasing the nucleophilic strength of the amine will increase the rate of the carbonyl-amine reaction but will have almost no effect on the position of the equilibrium.

These comments suggest that the amine-containing carbonyl-trapping drugs described herein should have particular promise for binding furanaldehydes, which are aromatic. These comments also suggest that doses of absorbable amine drugs may require in vivo concentrations in the range of 1:100 to 1:1,000 (carbonyl:amine) in order to achieve clinical effectiveness. This, in turn, suggests that therapeutic dosages may lie in the range of grams per day and that only drugs of particularly low toxicity will have human applications.

Feeney and coworkers (1975, pg. 144) also noted the phenomenon of Schiff base transimination, which occurs to a significant extent at neutral pH:



The existence of such non-enzymatic reversible transimination reactions is important within the context of this invention, as it suggests that in vivo both bound carbonyl agents, in addition to free carbonyl agents, may be sequestered by amine-containing drugs.

The small molecular weight, absorbable, primary amine compounds described herein have analogous behavior in vivo, as well as an additional characteristic which facilitates disposal as urine metabolites. All of these compounds contain a carboxylic acid group to facilitate uptake and processing by the kidneys.

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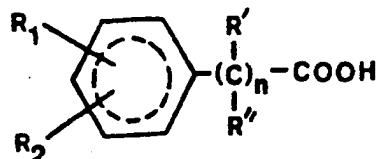
The metabolic fate of PABA in humans has been actively investigated and well reported in the biomedical literature (Young and coworkers, 1971; Howie and Bourke, 1979). It is so actively metabolized via several mechanisms and quantitatively removed in urine (Bingham and Cummings, 1983; Weizman and coworkers, 1985) that PABA excretion has become a widely recognized standard for measuring urinary clearance. Small amounts of PABA are normally present in the human diet. It is recognized as being a vitamin for many organisms and is classified as a member of the vitamin B complex (Scott and Robbins, 1942; Winitz and coworkers, 1970, pgs. 527-528; Smith, 1976, pg. 194). As a vitamin for human use PABA is commercially marketed in the dosage range of 5 to 550 mg/day.

(ii) Examples of Absorbable Drug Primary Agents

Primary agents of this invention are selected from the group consisting of six-carbon cyclic compounds containing a primary amino substituent group and a carboxylic substituent group wherein the carbon ring can be phenyl, cyclohexane, cyclohexene or cyclohexadiene. The carboxyl group can be attached directly to the carbon ring, or can be separated from the ring by one carbon atom. The primary amino group can be attached directly to the carbon ring, or it can be part of a larger functional group that is a substituent of the ring, either in the omega position or at some intermediate point in the larger functional group. The primary amino group may be attached to the six-member carbon ring at the p-, o- or m-position relative to the carboxyl substituent group. p-Aminobenzoic acid (PABA) is an example of this group. p-Aminobenzoic acid is known as a water-soluble B vitamin, and several published studies have presented evidence to the effect that PABA functions, in part, as a weak anti-oxidant and a weak free radical trapping agent (Maksimov and Rebachuk, 1985, Table 2; Pryor and coworkers, 1976, pg. 201). In so far as benzoic acid or derivatives thereof have been recognized as anti-oxidants or free radical trapping agents, their mechanism of action is understood to consist of hydroxyl radical trapping by the benzene ring (Grootveld and Halliwell, 1988; Halliwell and Gutteridge, 1985, pgs. 105 and 130; Richmond and coworkers, 1981; Repine and coworkers, 1979, pg. 1642). This

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has been explicitly demonstrated for PABA (Nakken, 1964, pgs. 446, 448, 454-457; Nakken and Pihl, 1966, pgs. 21, 22, 24, 25 and 28).

In addition to any carboxylic acid primary agent listed herein as useful in the present invention, the pharmaceutically acceptable salt forms, pharmaceutically acceptable ester and amide derivatives thereof are useful. The class of primary agents of the present invention are water soluble compounds (molecular weight range 100 to 1,400) of the formula:



wherein R_1 is $-NH_2$; -aminoalkyl having 1-10 carbons; $-NHC(=NH)NH_2$; $-(CH_2)_nNHC(=NH)NH_2$ wherein n is 1-10; $C(=NH)NH_2$; $-(CH_2)_n-CH=NC(=NH)NH_2$ wherein n is 1-10; $-NHC(=NH)NHNH_2$; $-(CH_2)_nNHC(=NH)NHNH_2$ wherein n is 1-10; $-(CH_2)_n-CH=NC(=NH)NHNH_2$ wherein n is 1-10; $-NHNHC(=NH)NH_2$; $-(CH_2)_n-NHNHC(=NH)NH_2$ wherein n is 1-10; and $-(CH_2)_n-CH=N-NHC(=NH)NH_2$ wherein n is 1-10;

R_2 is H ; $-OH$; $-O-CH_3$; $-O-R'$ wherein R' is alkyl of 2-10 carbons; aminoalkyl wherein the alkyl group is 1-10 carbons; $-SO_3H$; $-CH_3$; and $-(CH_2)_nCH_3$ wherein n is 1-10;

R' and R'' are $-H$, OH or CH_3 ; and n is 0 or 1.

These compounds are used in the compositions of the present invention in dosage levels of from 600 mg to about 20 gm per day in one or more divided doses, preferably from about 1 gm to about 20 gm per day, more preferably from about 3 gm to about 20 gm per day, and most preferably from about 6 gm to about 20 gm per day. Alternatively expressed, the dosage of these compounds is in the range of 15 mg/kg daily to about 800 mg/kg daily, preferably 30 mg/kg daily to about 800 mg/kg, more preferably 60 mg/kg daily to about 800 mg/kg, and most preferably 120 mg/kg daily to about 800 mg/kg.

(iii) Mechanism of Action of Nonabsorbable Primary Amine and Amine-Related Polymeric Co-Agents

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The presence of aldehydes and ketones in the human diet (Dunlop and Peters, 1953, pgs. 280, 308 and 403; Rice, 1972; Schauenstein and Esterbauer, 1977, pgs. 181-194; Shimizu and Watanabe, 1979; Baltes, 1985; Lever and coworkers, 1985) may be a factor which may put a patient suffering from a chronic inflammatory disease further at risk. This might be especially important for victims of chronic autoimmune gastritis, ileitis and colitis, as the damaging effects of inflammation site carbonyl compounds may be accentuated by direct exposure to dietary carbonyl agents.

As such, it is apparent that the diet is a significant source of carbonyl agents, and their presence may be a contributing factor in the etiology of chronic inflammatory diseases. Toxic properties of furanaldehyde derivatives have been demonstrated in both in vivo and in vitro studies (Konecki and coworkers, 1974; Ulbricht and coworkers, 1984). The nonabsorbable dietary supplements such as those defined below can be of health benefit by virtue of their ability to covalently trap dietary aldehydes and ketones. The agents described in this section can accomplish this function because they bear primary amine groups or derivatives thereof. As large molecular weight molecules which are non-digestible they have the capacity to pass through the digestive tract, acting in effect as another form of dietary fiber. These nonabsorbable polyamine trapping substances may be divided into three classes; naturally occurring polyamine polysaccharides, chemical derivatives of naturally occurring polysaccharides, and synthetic polyamine polymers.

The fate of malondialdehyde given orally to rats may serve as an example of the metabolism of dietary aldehydes, and how an understanding of this process can be used to define nonabsorbable carbonyl-trapping drugs. Studies by Draper and coworkers (1986) demonstrated that the primary form of "bound" MDA in rat or human urine is *N*- α -acetyl- ϵ -(2-propenal)lysine. This is the biologically acetylated derivative of the MDA-lysine adduct *N*- ϵ -(2-propenal)lysine. Draper and coworkers (1986) were able to generate *N*- ϵ -(2-propenal)lysine in vitro by exposing beef muscle protein to MDA, followed by treatment with pepsin and hog intestinal juice. This indicates that the

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ϵ -amino groups of dietary protein lysine residues can covalently bind dietary aldehyde under conditions found in the intestinal tract. As such, chemically analogous primary amine groups on nonabsorbable drugs should also be capable of covalently binding dietary aldehydes under conditions to be found in the intestinal tract. In this case, however, the bound carbonyl species would be excreted in the feces, thus preventing subsequent in vivo exposure to dietary carbonyl agents.

In their study Draper and coworkers noted that *N*- α -acetyl- ϵ -(2-propenal)lysine was found in urine of fasted rats or animals fed on MDA-free diets, indicating that the MDA-lysine adduct also forms in vivo. These investigators referred to earlier work which demonstrated that the MDA concentration normally found in food is in the range of <0.1 to 10 ppm (0.1 to 10 μ M), which gives some idea of dietary aldehyde concentrations.

(iv) Examples of Nonabsorbable Drug Products Useful in the Method of the Present Invention

(a) Naturally Occurring Amine-Containing Polysaccharides

Any naturally occurring polysaccharide featuring β -1,2, β -1,3, β -1,4 and/or β -1,6 linkages which contains aminosugars may be regarded as a non-digestible, potentially active carbonyl trapping agent. The chitin class of biopolymers may be cited as an example of such an agent, having the general structure of

poly- β -(1 \rightarrow 4)-*N*-acetyl-D-glucosamine

A form of microcrystalline chitin has been described in which some of the acetyl groups have been removed, revealing free amine groups (Austin and coworkers, 1981, pg. 750). Chitins obtained from different sources feature different degrees of amine deacetylation (Austin and coworkers, 1981, pg. 752).

(b) Chemical Derivatives of Naturally Occurring Polysaccharides

Various pretreatment procedures may be applied to naturally occurring polysaccharides prior to generation of chemical derivatives. Generation of microcrystalline polysaccharides is one example of such a pretreatment procedure. As applied to cellulose or chitin (Valpani, 1988, pg. 389), this yields a colloidal processed form of polysaccharide featuring high

"POLY"

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porosity and enhanced susceptibility to chemical reactions. Generation of "microfibrillated" cellulose or chitin is another example of a pretreatment procedure which produces enhanced surface area, increased water retention capacity and enhanced chemical accessibility (Yalpani, 1988, pg. 390). Use of strong ($> 18\%$) sodium hydroxide is still another recognized pretreatment, or activation, procedure found to be helpful as a starting point for preparing chemical derivatives of polysaccharides (Yalpani, 1988, pg. 214).

(b)(1) Deacetylation of Naturally Occurring Polysaccharides.

A variety of polysaccharides have been identified which are rich in *N*-acetylated residues. Upon chemical deacetylation these carbohydrates yield high molecular weight derivatives bearing primary amine groups directly linked to sugar carbons, that is, no sidearm spacer units present.

i. Chitosan. This is the deacylated form of chitin. As described in the Merck Index (Budavari and coworkers, 1989, pg. 316) chitin is a cellulose-like biopolymer the composition of which consists mostly of *N*-acetyl-D-glucosamine residues covalently linked by β -1,4 bonds. Chemical deacylation removes acetate, generating primary amine groups still covalently bound to the polysaccharide. Chitosan has recognized uses in water treatment, in photographic emulsions, and in improving the dyability of synthetic fabrics and fibers. The free amine groups in this substance also give it chelating properties (Austin and coworkers, 1981).

ii. Chondroitin sulfate. This is a mucopolysaccharide found commonly in mammalian tissue. It consists of repeating disaccharide units, each of which has a D-glucuronic acid residue β -1,4 linked to an *N*-acetylchondrosine residue (Budavari and coworkers, 1989, pg. 344).

iii. Hyaluronic acid. This mucopolysaccharide is also found commonly in mammalian tissues. It consists of glucuronic acid and glucosamine residues bound by β -1,3 and β -1,4 linkages (Budavari and coworkers, 1989, pp. 751-752).

iv. Keratan sulfate. This mammalian glycosaminoglycan consists of a repeating disaccharide unit of a C-6 sulfated C-2 *N*-acetylated sugar residue and a galactose residue linked by β -1,4 bonds (Yalpani, 1988, pp. 27-28).

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(b) (2) Chemical Amination of Polysaccharides

i. 2-Amino-2-deoxycellulose. Cellulose can be aminated by a process of selective oxidation, oximation and subsequent reduction with lithium aluminum hydride (Yalpani, 1988, pp. 281-282).

ii. Alternative amination procedures. Aminodeoxy polysaccharides can also be prepared via azide or hydrazide intermediates or by reductive amination using sodium cyanoborohydride (Yalpani, 1988, pg. 281). Besides being applied to cellulose, other non-digestible polysaccharides such as curdlan (Yalpani, 1988, pg. 22) may be aminated by such chemical procedures.

iii. 3-Aminopropylcellulose. Reaction of cyanoethylcellulose with borane-tetrahydrofuran or borane-dimethyl sulfide complexes in tetrahydrofuran generates 3-aminopropylcellulose (Yalpani, 1988, pgs. 250 and 255). In this derivative each primary amine group is at the end of a three carbon sidearm.

iv. Aminoethylcellulose. This chemical has been previously marketed as an anion exchange column chromatography resin (Sigma Chemical Co. catalog, Feb. 1981) and used as such in protein purification studies (Fasold, 1975, pp 481-482).

v. Other aminoalkyl-, amino(hydroxyalkyl)-, aminoalkyl-ether- and amino(hydroxyalkyl)-ether- derivatives of cellulose, chitin and other naturally occurring non-digestible carbohydrates. Noting that the chemical methodology for producing such derivatives is documented in public domain literature, the biomedical application of such derivatives for therapeutic purposes described herein is also claimed. This would include:

aminoalkyl derivatives of the formula

$H_2N-(CH_2)_n-[carbohydrate]$ where $n = 1 - 30$, including alkyl isomers;

amino(hydroxyalkyl)- derivatives of the formula

$H_2N-(CH_2)_m-CHOH-(CH_2)_n-[carbohydrate]$, where $m = 0 - 15$
 $n = 0 - 15$;

aminoalkyl-ether- derivatives of the formula

$H_2N-(CH_2)_n-O-[carbohydrate]$, where $n = 1 - 30$; and

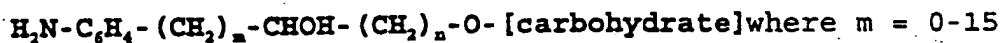
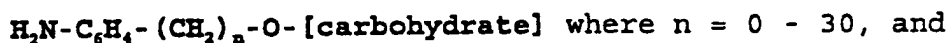
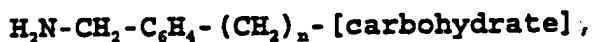
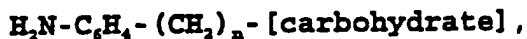
amino(hydroxyalkyl)-ether- derivatives of the formula

$H_2N-(CH_2)_m-CHOH-(CH_2)_n-O-[carbohydrate]$, where $m = 0 - 15$

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n = 0 - 15

vi. Aminobenzyl- derivatives of cellulose, chitin or other naturally occurring non-digestible carbohydrates. As the aromatic amine group is a weaker base than its aliphatic counterpart, this class of nonabsorbable amines should be less chemically active than amino- and aminoalkyl- derivatives described above. These derivatives are of the following general structures:



n = 0-15

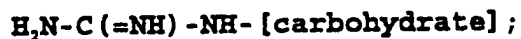
This includes p-, o- and m-benzene ring amino- and aminomethyl- isomers, and alkyl group isomers.

vii. guanidine and aminoguanidine derivatives of cellulose, chitin or other naturally occurring nonabsorbable carbohydrates selected from the group consisting of:



$H_2N-C(=NH)-(CH_2)_n-[carbohydrate]$, where n = 1-10, including hydrocarbon isomers and hydroxylated derivatives thereof;

$H_2N-C(=NH)-O-(CH_2)_n-[carbohydrate]$, where n = 1-10, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

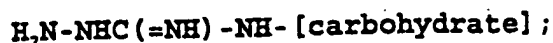


$H_2N-C(=NH)-NH-(CH_2)_n-[carbohydrate]$, where n = 1-10, including hydrocarbon isomers and hydroxylated derivatives thereof;

$H_2N-C(=NH)-NH-(CH_2)_n-O-[carbohydrate]$, where n = 1-10, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$H_2N-C(=NH)-N=CH-(CH_2)_n-[carbohydrate]$, where n = 1-10, including hydrocarbon isomers and hydroxylated derivatives thereof;

$H_2N-C(=NH)-N=CH-(CH_2)_n-O-[carbohydrate]$, where n = 1-10, including hydrocarbon isomers and hydroxylated derivatives thereof;



$H_2N-NHC(=NH)-NH-(CH_2)_n$ -^{3/}[carbohydrate], where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$H_2N-NHC(=NH)-NH-(CH_2)_n-O$ -[carbohydrate], where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$H_2N-NHC(=NH)-N=CH-(CH_2)_n$ -[carbohydrate], where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$H_2N-NHC(=NH)-N=CH-(CH_2)_n-O$ -[carbohydrate], where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$H_2N-C(=NH)-NH-NH$ -[carbohydrate];

$H_2N-C(=NH)-NH-NH-(CH_2)_n$ -[carbohydrate], where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$H_2N-C(=NH)-NH-NH-(CH_2)_n-O$ -[carbohydrate], where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$H_2N-C(=NH)-NH-N=CH-(CH_2)_n$ -[carbohydrate], where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$H_2N-C(=NH)-NH-N=CH-(CH_2)_n-O$ -[carbohydrate], where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

(b) (3) Aminated Sucrose Polyesters

Mixtures of fatty acid hexa-, hepta- and octaesters of sucrose, known as sucrose polyester, are not hydrolyzed by pancreatic lipase enzymes and are not absorbed in the intestine (Jandacek, 1984). It is disclosed and claimed herein that primary amine, aminoguanidine and guanidine derivatives of sucrose polyesters are of benefit in reduction of dietary carbonyl substances, analogous to the proposed action of other nonabsorbable agents described herein. Such derivatives of sucrose polyesters would include structures in which the carbonyl trapping functional group is in the ω -, $\omega-1$ or other isomeric position(s) within the fatty acyl chains, fatty acyl chains having more than one nitrogen functional group and fatty acyl chains having hydroxyl groups. Such aminated

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sucrose polyesters may be used in pure form as a dietary supplement, or may be prepared as a coating on a particulate carrier such as, for example, cellulose or styrene divinylbenzene copolymer resin.

(c) Synthetic Polyamine Polymers

(c) (1) Synthetic polysaccharides consisting partly or entirely of aminosugars bound by β -1,2, β -1,3, β -1,4 and/or β -1,6 linkages may be regarded as nonabsorbable carbonyl trapping agents.

(c) (2) Mixed polysaccharide polymeric derivatives. Primary amine, aminoalkyl (one to ten carbons per alkyl group), amino-hydroxyalkyl (one to ten carbons per alkyl group and one to ten-hydroxyl groups per alkyl group), aminoguanidine, aminoguanidiny-alkyl (one to ten carbons per alkyl group), amino-alkylguanidiny-alkyl (one to ten carbons per alkyl group), guanidine, aminobenzene and aminoalkylbenzene (one to ten carbons per alkyl group) functional groups may be covalently attached to matrices such as, for example, epi-chlorohydrin copolymers of cellulose or chitin. Functional group spacer groups may include alkene as well as alkyl groups.

(c) (3) Non-polysaccharide polymeric derivatives. Primary amine, aminoalkyl (one to ten carbons per alkyl group), aminohydroxyalkyl (one to ten carbons per alkyl group and one to ten hydroxyl groups per alkyl group), aminoguanidine, aminoguanidiny-alkyl (one to ten carbons per alkyl group), aminoalkylguanidiny-alkyl (one to ten carbons per alkyl group), guanidine, aminobenzene and aminoalkylbenzene (one to ten carbons per alkyl group) functional groups may be covalently attached to a wide variety of synthetic non-digestible polymers. Functional group spacer groups may include alkene as well as alkyl groups. Like their sugar-based counterparts, these agents should be capable of reacting with dietary carbonyl compounds. Nitrogen-containing functional groups may be covalently attached to synthetic supports such as, for example, polystyrene, styrene-divinylbenzene copolymer, polyvinyl alcohol and crosslinked derivatives thereof.

These nonabsorbable polyamine compounds that sequester carbonyl substances present in the diet are used in the compositions of the present invention in dosage levels of from 600

mg to about 20 gm per day in one ³³ or more divided doses, preferably from about 1 gm to about 20 gm per day, more preferably from about 3 gm to about 20 gm per day, and most preferably from about 6 gm to about 20 gm per day. Alternatively expressed, the dosage of these compounds is in the range of 15 mg/kg daily to about 800 mg/kg daily, preferably 30 mg/kg daily to about 800 mg/kg, more preferably 60 mg/kg daily to about 800mg/kg, and most preferably 120 mg/kg daily to about 800 mg/kg.

(v) Co-Administration of Anti-Oxidants and Lipid Peroxidation Inhibitors

As regards the use of anti-oxidant and lipid peroxidation inhibitor co-agents, vitamin co-agents, co-agents which are metabolites at risk of depletion, sulfhydryl co-agents, and co-agents which may facilitate glutathione activity, it is assumed herein that these substances are administered orally unless stated otherwise. Dosage ranges for these co-agents refer to human use and may be adjusted accordingly for use by other mammals on a per kilogram basis. It is claimed herein that the therapeutic value of the primary amine agents of the present invention can be maximized by administration in conjunction with recognized anti-oxidant free radical trapping compounds such as α -tocopherol (Ferrari and coworkers, 1991, pg. 97S; Stuckey, 1968, pp. 214-215), dosage range from 100 I. U. daily to 3,500 I. U. daily, or other agents previously recognized as adjuncts which facilitate in vivo capability to inhibit lipid peroxidation. The dosage range noted above for α -tocopherol is also claimed for other vitamin E derivatives such as β -tocopherol, γ -tocopherol, δ -tocopherol, ϵ -tocopherol, ζ_1 -tocopherol, ζ_2 -tocopherol and η -tocopherol, as well as ester derivatives thereof such as the corresponding acetate, succinate and nicotinate forms.

Citric acid, dosage range from 200 mg daily to 20 gm daily, may be included in this category of co-administered agents, as it is recognized as having anti-oxidant properties (Merck Index, Budavari, 1989, pg. 363). Alternatively, this co-agent may be consumed as a combination of potassium citrate monohydrate and citric acid monohydrate in a weight ratio of 3.3 to 1, or other weight ratio selected so as to alkalize

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a composition. Citric acid is also recognized as an inhibitor of Maillard reactions (Stuckey, 1968, pg. 210).

In a published list of agents which function to supplement the chain-breaking anti-oxidant property of vitamin E, Tappel (1970, pg. 1138) mentioned ubiquinol, seleno-amino acids and sulfhydryl compounds (e.g., glutathione, sulfhydryl proteins, cysteine and methionine). An intravenous, intramuscular, subcutaneous or oral dosage range from 10 mg daily to 500 mg daily for the class of ubiquinols, coenzyme Q_n where n = 1 - 12, is proposed herein. An intravenous, intramuscular, subcutaneous or oral dosage range from 10 mg daily to 500 mg daily for glutathione is proposed herein. Other substances in this general group include butylated-hydroxytoluene (Frankel, 1987, pg. 81), dosage range from 10 mg daily to 1 gm daily; butylated hydroxyanisole (Sies, 1991, pg. 32S), dosage range from 5 mg daily to 40 mg daily; propyl gallate (Verhagen and coworkers, 1991, pg. 113), dosage range from 10 mg daily to 1 gm daily; dodecylgallate (Verhagen and coworkers, 1991, pg. 113), dosage range from 10 mg daily to 1 gm daily; tert-butylhydroquinone (Verhagen and coworkers, 1991, pg. 113), dosage range from 10 mg daily to 1 gm daily; β -carotene, dosage range from 20 mg daily to 300 mg daily (Frankel, 1987, pg. 82); dihydrolipoic acid (Sies, 1991, pgs. 33S and 36S), intravenous, intramuscular, subcutaneous or oral dosage range from 10 mg daily to 500 mg daily; N-acetyl-cysteine (Le Guen and coworkers, 1992), dosage range from 10 mg/kg daily to 150 mg/kg daily; prostaglandin B₁ oligomers (also known as polymeric 15-keto prostaglandin B or PGB_x), intravenous, intramuscular, subcutaneous or oral dosage range from 5 mg/kg daily to 400 mg/kg daily; 2-aminomethyl-4-tert-butyl-6-iodophenol, dosage range from 0.5 mg/kg daily to 600 mg/kg daily (Swingle and coworkers, 1985, pg. 120); 2-aminomethyl-4-tert-butyl-6-propionylphenol, dosage range from 20 mg/kg daily to 500 mg/kg daily (Swingle and coworkers, 1985, pgs. 120-121); 2,6-di-tert-butyl-4-[2'-thenoyl]phenol, dosage range from 3 mg/kg daily to 300 mg/kg daily (Swingle and coworkers, 1985, pg. 121); N,N'-diphenyl-p-phenylenediamine, dosage range from 5 mg/kg daily to 500 mg/kg daily (Swingle and coworkers, 1985, pg. 118); ethoxyquin, dosage range from 5 mg/kg daily to 500

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mg/kg daily (Swingle and coworkers, 1985, pg. 118); probucol, a synthetic anti-oxidant (Halliwell, 1991, pg. 586), dosage range from 25 mg daily to 1 gm daily; ebselen, intravenous, intramuscular, subcutaneous or oral dosage range from 5 mg/kg daily to 500 mg/kg daily; 5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-3-(dimethylamino)-4-thiazolidinone (LY221068; Panetta and coworkers, 1991), dosage range from 1 mg/kg daily to 100 mg/kg daily; 5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-3-(methylamino)-4-thiazolidinone (LY269415, Panetta and coworkers, 1991), dosage range from 1 mg/kg daily to 100 mg/kg daily; D-myoinositol-1.2.6-trisphosphate (Claxson and coworkers, 1990), intravenous, intramuscular, subcutaneous or oral dosage range from 10 mg/kg daily to 1.5 gm/kg daily; nordihydroguaiaretic acid, intravenous, intramuscular, subcutaneous or oral dosage range from 100 mg/kg daily to 2 gm/kg daily; deferoxamine mesylate, intravenous, intramuscular or subcutaneous dosage range from 100 mg daily to 2 gm daily; tirilazad mesylate (U-74006F), intravenous, intramuscular or subcutaneous dosage range from 150 µg/kg/hr to 15 mg/kg/hr; derivative of tirilazad in which the steroid portion of the chemical structure has been replaced with the tetramethyl chroman portion of d-α tocopherol (U78517F, Upjohn), intravenous, intravenous or subcutaneous dosage range from 150 µg/kg/hr to 15 mg/kg/hr; trimetazidine, dosage range from 100 µg/kg daily to 3.0 mg/kg daily; N,N'-dimethylthiourea (Repine, 1991), intravenous, intramuscular, subcutaneous or oral dosage range from 5 mg/kg daily to 100 mg/kg daily; and 2-(2-hydroxy-4-methylphenyl)aminothiazole hydrochloride (Bonne and coworkers, 1990), dosage range from 0.1 mg/kg daily to 50 mg/kg daily. Selenium may also be included in this group, dosage range from 25 µg daily to 0.5 mg daily, as it has recognized indirect anti-oxidant properties (Stuckey, 1968, pg. 236). Some in vivo experimental data has been presented which indicates that α-tocopherol; butylated-hydroxytoluene; propyl gallate; 2-aminomethyl-4-tert-butyl-6-iodophenol; 2-aminomethyl-4-tert-butyl-6-propionylphenol; 2,6-di-tert-butyl-4-[2'-thenoyl]-phenol; N,N'-diphenyl-p-phenylenediamine; ethoxyquin; ebselen; 5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-3-(dimethylamino)-4-thiazo-

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lidinone; 5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-methylene]-3-(methylamino)-4-thiazolidinone; nordihydroguaiaretic acid; 2-(2-hydroxy-4-methylphenyl)aminothiazole hydrochloride; and D-myoinositol-1.2.6-trisphosphate possess both anti-inflammatory and anti-oxidant properties (Swingle and coworkers, 1985, pgs. 114, and 118-121; Claxson and coworkers, 1990; Schmidt and Bayer, 1990, pg. 149; Honkanen and coworkers, 1990, pg. 190; Gado and Gigler, 1991; Panetta and coworkers, 1991; Parnham and coworkers, 1991).

(vi) Prophylactic Vitamin Co-Administration

It is yet still another object of this invention that the safety and effectiveness of the products described herein may be optimized by co-administration of vitamins which may be inadvertently depleted by the treatment or which may otherwise contribute to the clinical effectiveness of the compositions. This group includes:

- retinol, dermal, subcutaneous, intravenous, intramuscular or oral dosage range from 10 $\mu\text{g/kg}$ daily to 1 mg/kg daily;

- vitamin A aldehyde (retinal), dermal, subcutaneous, intravenous, intramuscular or oral dosage range from 10 $\mu\text{g/kg}$ daily to 1 mg/kg daily;

- vitamin A acid (retinoic acid), dermal, subcutaneous, intravenous, intramuscular or oral dosage range from 10 $\mu\text{g/kg}$ daily to 1 mg/kg daily;

- retinyl acetate, dermal, subcutaneous, intravenous, intramuscular or oral dosage range from 10 $\mu\text{g/kg}$ daily to 1 mg/kg daily;

- vitamin B₁ (thiamine HCl), dosage range from 1 mg daily to 1.5 gm daily;

- thiamine propyl disulfide, dosage range from 1 mg daily to 1.5 gm daily;

- thiamine disulfide, dosage range from 1 mg daily to 1.5 gm daily;

- thiamine disulfide O,O-diisobutyrate, dosage range from 1 mg daily to 1.5 gm daily;

- thiamine disulfide hydrochloride, dosage range from 1 mg daily to 1.5 gm daily;

- thiamine disulfide phosphate, dosage range from 1 mg daily to 1.5 gm daily;

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-thiamine mononitrate, dosage range from 1 mg daily to 1.5 gm daily;

-thiamine 1,5-salt, dosage range from 1 mg daily to 1.5 gm daily;

-thiamine phosphoric acid ester chloride, dosage range from 1 mg daily to 1.5 gm daily;

-thiamine phosphoric acid ester phosphate salt, dosage range from 1 mg daily to 1.5 gm daily;

-thiamine triphosphoric acid ester, dosage range from 1 mg daily to 1.5 gm daily;

-vitamin B₂ (riboflavin), dosage range from 1 mg daily to 1 gm daily;

-riboflavin tetrabutyrates, dosage range from 1 mg daily to 1 gm daily;

-riboflavine 5'-phosphate ester monosodium salt, dosage range from 1 mg daily to 1 gm daily;

-vitamin B₆ (pyridoxine HCl), dosage range from 10 mg daily to 1.75 gm daily;

-pyridoxal, dosage range from 10 mg daily to 1.75 gm daily;

-pyridoxal HCl, dosage range from 10 mg daily to 1.75 gm daily;

-pyridoxal 5-phosphate, dosage range from 10 mg daily to 1.75 gm daily;

-pyridoxal 5-phosphate calcium salt, dosage range from 10 mg daily to 1.75 gm daily;

-pyridoxamine, dosage range from 10 mg daily to 1.75 gm daily;

-pyridoxamine dihydrochloride, dosage range from 10 mg daily to 1.75 gm daily;

-pyridoxamine phosphate, dosage range from 10 mg daily to 1.75 gm daily;

-vitamin B₁₂ (cyanocobalamin), intravenous or oral dosage range from 1 µg daily to 1 mg daily;

-methyl vitamin B₁₂ (co-methylcobalamin), intravenous or oral dosage range from 1 µg daily to 1 mg daily;

-vitamin D₂, dosage range from 400 units daily to 40,000 units daily;

-vitamin D₃, dosage range from 400 units daily to 40,000

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units daily;

-vitamin D₄, dosage range from 400 units daily to 40,000 units daily;

-vitamin H (biotin), intravenous, subcutaneous or oral dosage range from 150 µg daily to 200 mg daily;

-vitamin K₁ (phytonadione), intravenous, subcutaneous or oral dosage range from 100 µg daily to 100 mg daily;

-diacetyl dihydro vitamin K₁, intravenous, subcutaneous or oral dosage range from 100 µg daily to 100 mg daily;

-vitamin K₁ oxide, intravenous, subcutaneous or oral dosage range from 100 µg daily to 100 mg daily;

-vitamin(s) K₂ (menaquinones), intravenous, subcutaneous or oral dosage range from 100 µg daily to 100 mg;

-vitamin K_{2(35)}}, intravenous, subcutaneous or oral dosage range from 100 µg daily to 100 mg daily;

-vitamin K_{2(35)}} dihydrodiacetate, intravenous, subcutaneous or oral dosage range from 100 µg daily to 100 mg daily;

-vitamin K_{2(30)}}, intravenous, subcutaneous or oral dosage range from 100 µg daily to 100 mg daily;

-vitamin K_{2(30)}} dihydrodiacetate, intravenous, subcutaneous or oral dosage range from 100 µg daily to 100 mg daily;

-vitamin K₃, intravenous, subcutaneous or oral dosage range from 100 µg daily to 100 mg daily;

-vitamin K₃ hydrochloride, intravenous, subcutaneous or oral dosage range from 100 µg daily to 100 mg daily;

-N-acetyl vitamin K₃, intravenous, subcutaneous or oral dosage range from 100 µg daily to 100 mg daily;

-vitamin K₆, intravenous, subcutaneous or oral dosage range from 100 µg daily to 100 mg daily;

-vitamin K₆ dihydrochloride, intravenous, subcutaneous or oral dosage range from 100 µg daily to 100 mg daily;

-vitamin K₇, intravenous, subcutaneous or oral dosage range from 100 µg daily to 100 mg daily;

-vitamin K₇ hydrochloride, intravenous, subcutaneous or oral dosage range from 100 µg daily to 100 mg daily;

-vitamin K-S(II), intravenous, subcutaneous or oral dosage range from 100 µg daily to 100 mg daily;

-vitamin L₁, dosage range from 10 mg daily to 500 mg daily;

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- vitamin L₂, dosage range from 10 mg daily to 500 mg daily;
 - vitamin U, dosage range from 25 mg daily to 1 gm daily;
 - methylmethioninesulfonium bromide (bromide analog of vitamin U), dosage range from 25 mg daily to 1 gm daily;
 - α -carotene, dosage range from 20 mg daily to 300 mg daily;
 - β -carotene, dosage range from 20 mg daily to 300 mg daily;
 - γ -carotene, dosage range from 20 mg daily to 300 mg daily;
 - ω -carotene, dosage range from 20 mg daily to 300 mg daily;
 - ψ -, ψ -carotene (also known as lycopene; Sies, 1991, pg. 33S), dosage range from 5 mg daily to 300 mg daily;
 - 7,7',8,8',11,12-hexahydro- ψ -, ψ -carotene (also known as phytofluene; Halliwell, 1991, pg. 576), dosage range from 5 mg daily to 300 mg daily;
 - L-carnitine (vitamin B_T; Carnitor, Sigma-Tau Pharmaceuticals), dosage range from 100 mg daily to 3 gm daily;
 - acetyl-L-carnitine, dosage range from 100 mg daily to 3 gm daily;
 - folic acid (vitamin Bc), dosage range from 0.5 mg daily to 50 mg daily;
 - folinic acid, dosage range from 0.5 mg daily to 50 mg daily;
 - folinic acid calcium salt pentahydrate, dosage range from 0.5 mg daily to 50 mg daily;
 - niacinamide, dosage range from 100 mg daily to 10 gm daily;
 - nicotinic acid (vitamin B₃; Nicolar, Rhone-Poulenc Rorer), dosage range from 100 mg daily to 10 gm daily;
 - nicotinic acid sodium salt sesquihydrate, dosage range from 100 mg daily to 10 gm daily;
 - nicotinic acid monoethanolamine salt, dosage range from 100 mg daily to 10 gm daily;
 - pantothenic acid, dosage range from 5 mg daily to 2 gm daily;
 - pantothenic acid sodium salt, dosage range from 5 mg

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daily to 2 gm daily; and

-pantothenic acid calcium salt, dosage range from 5 mg daily to 2 gm daily.

Several of these vitamins possess carbonyl functional groups and thus may be depleted by clinical use of the present invention. Others have a reported anti-oxidant effect, such as the carotenes, or may possess an anti-inflammatory effect, such as carnitine (Elliott and coworkers, 1991), retinoic acid (Fumarulo and coworkers, 1991) and retinyl acetate (Fumarulo and coworkers, 1991).

(vii) Co-Administration of Metabolites at Risk of Depletion

It is another object of this invention that the safety and effectiveness of the products described herein may be optimized by co-administration of other metabolites, such as glycine, which may be depleted within the body during long term drug use. Use of glycine within the dosage range of from 1 gm daily to 20 gm daily is claimed herein. As many of the absorbable amine drugs described herein are excreted from the body as glycine conjugates, co-administration of glycine may be advisable. Coenzyme A is a required cofactor for hippuricase, the liver enzyme which adds glycine to benzoic acid derivatives. Activity of hippuricase in glycinating some of the absorbable carbonyl-trapping drugs described herein may sequester a disproportionate fraction of the endogenous coenzyme A pool. Hence co-administration of pantothenic acid, a metabolic precursor of coenzyme A, may also serve to optimize the therapeutic procedures described herein. A dosage range of from 5 mg daily to 2 gm daily for pantothenic acid is claimed herein.

(viii) Co-Administration of Sulfhydryl Agents

Noting the well documented ability of carbonyl agents to react with sulfhydryl groups (Jellum and coworkers, 1973), it is a further object of this invention that L-methionine, dosage range from 200 mg daily to 4 gm daily and homocysteine, dosage range from 200 mg daily to 2 gm daily may also be of clinical benefit as absorbable drugs capable of covalently binding aldehyde or ketone agents. Homocysteine contains a free sulfhydryl group. Likewise, acetyl-homocysteine thio-lactone, intravenous, intramuscular, subcutaneous or oral

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dosage range from 0.5 mg/kg daily to 25 mg/kg daily may also be included in this group. Methionine is converted in vivo to homocysteine by several enzymatic reactions which remove a methyl group. L-Methionine also has a demonstrated ability to scavenge hypochlorous acid, a reactive oxygen specie which may contribute to the degradation of hyaluronic acid seen in rheumatoid arthritis (Saari and coworkers, 1993, pgs. 404 and 408). Thiocctic acid, also known as α -lipoic acid, is also included in this category in a dosage range from 10 mg daily to 500 mg daily, including its sodium salt and ethylenediamine derivatives, as its structure includes a disulfide group. This agent, a recognized growth factor (Budavari and coworkers, 1989, pg. 1469), may tend to be depleted in the tissues of patients having chronic inflammatory diseases involving etiologies which include dysfunction of aldehyde and/or ketone metabolism. The ability of acetaldehyde to combine with thiocctic acid, thus deactivating it, has been reported (Smith, 1976, pg. 195).

(ix) Co-Administration of Agents Which May Facilitate Glutathione Activity

In addition, the present invention includes use of various co-agents which may facilitate glutathione activity. Use of N-acetylcysteine (Dansette and coworkers, 1990), dosage range from 10 mg/kg daily to 150 mg/kg daily, has been reported to increase the levels of plasma cysteine, plasma glutathione and red blood cell glutathione (Bernard, 1991), and to induce a 100-fold increase in myocardial glutathione subsequent to experimental ischemia and reperfusion (Ferrari and coworkers, 1991). N-Acetylcysteine reacts with hypochlorous acid, HO \cdot and H $_2$ O $_2$ (Bernard, 1991), as well as with reactive aldehydes found in tobacco smoke (Ohman and coworkers, 1992). Other substances in this class include L-2-oxothiazolidine-4-carboxylic acid, reported to hydrolyse in vivo to cysteine (Halliwell, 1991, pg. 590), dosage range from 0.3 mmol/kg daily to 3 mmol/kg daily; timonacic, also known as 4-thiazolidinecarboxylic acid (Dansette and coworkers, 1990), dosage range from 10 mg daily to 500 mg daily; cysteamine (Dansette and coworkers, 1990), dosage range from 200 mg daily to 4 gm daily; lipoamide derivatives (Dansette and coworkers,

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1990) such as malotilate (Kantec), dosage range from 100 mg daily to 2 gm daily; sulfarlem (ADT; Dansette and coworkers, 1990), intravenous, intramuscular, subcutaneous or oral dosage range from 100 mg/kg daily to 1 gm/kg daily; and oltipraz (Dansette and coworkers, 1990), intravenous, intramuscular, subcutaneous or oral dosage range from 100 mg/kg daily to 1 gm/kg daily, as these co-agents may further serve to improve the invention described herein.

(x) Factors Affecting Daily Dosage Schedule

A daily protocol of amine and amine-related drug consumption, in combination with co-agents defined herein, may be defined such that drug products are administered in timed-release and/or color coded tablets or capsules, so as to facilitate patient compliance and maximize therapeutic value. Alternatively, a therapeutic composition may be incorporated into a foodstuff product, so as to encourage regular, long term patient compliance.

(xi) Therapeutic Utilization

As indicated above the present invention is intended for the treatment of chronic inflammatory diseases and is useful for this purpose in various animal species, e. g., rodents, cats, dogs, cattle, sheep, horses, pigs, monkeys and other primates.

Two case histories regarding human subjects may serve to illustrate the practical application of the invention originally disclosed in US Patent Application 07/906,909.

Case History One: Pearson and Shaw (1982, pg. 299) described the following summary of an arthritis patient taking vitamin E and vitamin A:

The correct dose of antioxidants for effective arthritis therapy must be determined by experimentation. The effective dose may be quite high. For example, a friend of ours who is a well-known artist in his fifties developed arthritis in his hands. This man's hands became so painful and stiff he could no longer use his fingers to remove the caps from his tubes of paint. He tried vitamin E at increasing dose levels. It was not until he got up to 10,000 I.U. of E and 20,000 I.U. of A per

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day that he obtained relief from the pain and crippling stiffness. His hands are now flexible and can be used to draw without difficulty. But they remain so only as long as our friend takes 10,000 I.U. of E and 20,000 I.U. of A a day, not less (he's tried).

This dosage of vitamin E far exceeds presently accepted levels of daily usage, which are generally regarded as being in the range of 400 I.U. per day. This particular combination of vitamins E and A, both lipophilic, would not be expected to inhibit any of the free radical reactions taking place in aqueous microenvironments. Nor would it chemically bind and thus deactivate any reactive aldehydes generated by the inflammatory process, as such aldehydes are water soluble.

Case History Two: Patient L.S. has a history of arthritis dating back to a serious automobile accident in 1980. By January of 1991 she had serious arthritic involvement of the lumbar spine and chronic hip and knee joint pain on a continuous basis. She had difficulty raising herself from a chair, required the assistance of a cane for activities as simple as walking from her front door to her car, was no longer able to go up or down a flight of stairs, and required use of a prescription analgesic drug every two hours during the night to sleep. She had participated in a program at the Pain Clinic of the University of Miami Medical School and at doctor's advice had used prescription drugs which included Clinoril (R) and Anaprox (R), both nonsteroidal anti-inflammatory agents. At the recommendation of this inventor, patient L.S. began taking 800 I.U. vitamin E, 1. gm of methionine and 1.1 gm PABA per day for two months. Subsequently, vitamin E and methionine usage remained the same and PABA usage was increased to 2.2 gm per day, with the protocol continued on an indefinite basis.

When previously examined by an orthopedics physician a diagnosis was established which included:

...Lumbar spine X-Rays in AP and lateral views show extensive degenerative arthritic changes at multiple levels of the lumbar spine...severe arthritic changes lumbar spine. Bursitis left greater trochanter clinically...She will always have a problem related to her

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underlying degenerative disease involving her lower back...She is favoring her left leg...Her straight leg raising is limited on the left side...

Ten weeks after after initiating this inventor's PABA/methionine/vitamin E protocol, patient L.S. reported that her arthritis-related pain was much decreased and her functional status much improved. By four months into use of this therapeutic protocol patient L.S. had stopped using her cane, had a walking gait which was much improved, had taken to raking leaves in the yard as a form of exercise, and no longer required nighttime analgesics to sleep. At twelve months on this protocol, patient L. S. reported climbing and descending a flight of stairs without difficulty, and her ability to climb stairs has continued to improve. When re-examined by her orthopedic physician, who was not informed of her use of the PABA/ methionine/vitamin E protocol, seven months after beginning therapy the doctor noted, in part:

This patient is markedly better. She has normal straight leg raising. She has no significant leg pain. She walks well on her toes and walks well on her heels now without any evidence of motor weakness. There is no limp present.

Unaware of the patient's collaborative effort with this inventor, the orthopedic physician was unable to provide an explanation of the marked improvement in the clinical status of patient L.S. At her office visit patient L. S. noted that she had stopped taking Anaprox, which her orthopedics physician had prescribed seven months earlier.

This inventor recognizes the novel and original combination of primary amine benzoic acid derivatives as a primary agent to be used with anti-oxidant free radical trapping co-agents as a type of composition likely to have increased, or possibly even synergistic properties for the treatment of chronic inflammatory diseases. This inventive strategy for the clinical treatment of these diseases has not been previously recognized.

PABA, many of the other amine primary agents, the anti-oxidant free radical trapping co-agents, substances related

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thereto and previously known medicaments described herein are chemicals which have been previously synthesized and described. Yet the present invention recognizes a new and novel combination of therapeutic properties, never recognized previously, and the clinical applications thereof. My original invention, as defined in US patent application 07/906,909, constitutes a significant and practical advancement of clinical therapeutic technology available for treating chronic inflammatory diseases, and the present invention constitutes a further practical extension of the original inventive concept.

(xii) Use of the Invention of US Patent Application 07/906,909
in Combination with Previously Known Medicaments

As summarized above, it is evident that presently available pharmaceutical technology for treatment of the diseases addressed herein is almost entirely symptomatic, as well as temporary and of partial clinical benefit, at best. The dosages of any of the known medicaments discussed herein, except those which are still the subjects of preliminary laboratory studies, are well known to those skilled in the art. Significant adverse side effects accompany many of these treatments, which limit their use. The present invention defines the use of previously recognized technology in combination with the invention originally described in US patent application 07/906,909, so as to achieve greater clinical effectiveness in treatment of these diseases. In using the therapeutic technology defined herein, physicians may achieve in some cases the clinical benefits of previously recognized drugs while using lower dosage levels, thus minimizing adverse side effects. Within the context of the present invention, it is important to note the documentation provided by Flood and coworkers (1988). Their findings indicate that when drugs are used in combination they may provide beneficial effect at reduced dosages which are ineffective when drugs are administered alone. This approach may permit wider and more effective use of previously recognized drug technology. It is acknowledged herein that for many of the previously known medicaments the optimum dosage must be determined on an individualized basis, and may be below or above the dosage range

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generally recognized for public use. It is to be understood that dosage ranges listed below refer to adult usage and that in particular cases it may be desirable to go beyond the dosage ranges noted below. Various oral compositions as noted below which exemplify the present invention may be formulated with additional components or coatings so as to function in a slow acting, delayed release manner. Except where stated otherwise, the drugs listed in the following examples are to be administered orally. It is understood, however, that various combinations of administration via oral route and administration via injected route or topical route may be envisioned for the compositions listed below.

Example 1

Clinical treatment of chronic gingivitis and/or chronic periodontitis can be improved by use of a composition, administered in various oral, topical, intravenous, intramuscular, subcutaneous and intralesional combinations, comprising from about 1 gm to about 20 gm of at least one primary therapeutic agent comprising a primary amine benzoic acid derivative having a molecular weight of from about 100 to about 1,400 Daltons, and optionally at least one substance selected from those noted above in section (v) through section (ix), and a medicament recognized as effective to treat chronic gingivitis and/or chronic periodontitis, such as, for example,

(a) antibiotics such as

penicillin G potassium (Pfizerpen, Roerig), intramuscular, intravenous, local infusion or intrathecal dosage range from one million units daily to twenty million units daily;

penicillin G benzathine and penicillin G procaine combination (Bicillin C-R, Wyeth-Ayerst Laboratories), intramuscular dosage range from 300,000 units to 2,400,000 units administered for one day or daily until subsidence of abnormally high body temperature;

penicillin V potassium (Veetids, Apothecon), dosage range from 500 mg daily to 2 gm daily;

erythromycin (E-Mycin, Boots Laboratories), dosage range from 250 mg daily to 5 gm daily;

amoxicillin (Amoxil, SmithKline Beecham), dosage range from 750 mg daily to 1.5 grams daily;

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amoxicillin in combination with clavulanate potassium (Augmentin, SmithKline Beecham), dosage range from 750 mg amoxicillin and 187.5 mg clavulanate potassium daily to 1.5 grams amoxicillin and 375 mg clavulanate potassium daily; tetracycline (Achromycin V, Lederle), dosage range from 500 mg daily to 2 gm daily; doxycycline (Vibramycin, Pfizer), dosage range from 50 mg daily to 300 mg daily; and minocycline (Minocin, Lederle), dosage range from 50 mg daily to 300 mg daily;

(b) nitroimidazoles such as metronidazole (Flagyl, Searle), dosage range from 250 mg daily to 2.5 gm daily;

(c) antiseptics such as chlorhexidine gluconate (Peridex oral rinse, Proctor & Gamble), one to three oral rinses per day;

(d) surfactants such as triclosan, as ingredient in mouthwash or toothpaste, dosage range of one to three applications of 0.01% to 5% solution or suspension daily; and sanguinarine, as ingredient in mouthwash or toothpaste, dosage range of one to three applications of 0.01% to 5% solution or suspension daily;

(e) ebselen, intravenous, intramuscular, subcutaneous or oral dosage range from 5 mg/kg daily to 500 mg/kg daily, or application of 1% to 25% topical compositions;

(f) nonsteroidal anti-inflammatory drugs administered orally including suprofen; dosage range from 5 mg/kg daily to 100 mg/kg daily; and

(g) locally administered corticosteroid preparations such as hydrocortisone acetate, 0.5% (Orabase HCA, Colgate-Hoyt/Gel-

Kam), topical application one to four times daily.

The following illustrate specific formulations according to the present invention.

p-aminobenzoic acid

1 gm

d- α -tocopheryl succinate	500 I.U.
penicillin G potassium	one million units
p-aminobenzoic acid, potassium salt	20 gm
N-acetylcysteine	10 gm
suprofen	5 gm
p-aminomethylbenzoic acid	5 gm
acetylhomocysteine thiolactone	1 gm
metronidazole	2 gm

Example 2

Clinical treatment of chronic autoimmune gastritis can be improved by use of a composition comprising from about 1 gm to about 20 gm of at least one primary therapeutic agent comprising a primary amine benzoic acid derivative having a molecular weight of from about 100 to about 1,400 Daltons, and optionally at least one substance selected from those noted above in section (v) through section (ix), and a medicament recognized as effective to treat autoimmune gastritis, such as, for example,

(a) sodium guaiazulene-3-sulfonate, dosage range from 1 mg/kg daily to 20 mg/kg daily; and

(b) ebselen, intravenous, intramuscular, subcutaneous or oral dosage range from 5 mg/kg daily to 500 mg/kg daily.

The following illustrate specific formulations according to the present invention.

4-amino-3-hydroxybenzoic acid	1 gm
mixed tocopherols	1,000 I.U.
sodium guaiazulene-3-sulfonate	75 mg
p-aminobenzoic acid, potassium salt	15 gm
L-Methionine	1 gm
sodium guaiazulene-3-sulfonate	1.5 gm
5-amino-2-hydroxybenzoic acid	5 gm
N,N'-diphenyl-p-phenylenediamine	5 gm
ebselen	5 gm

Example 3

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Clinical treatment of ileitis, including Crohn's disease can be improved by use of a composition comprising from about 1 gm to about 20 gm of at least one primary therapeutic agent comprising a primary amine benzoic acid derivative having a molecular weight of from about 100 to about 1,400 Daltons, and optionally at least one substance selected from those noted above in section (v) through section (ix), and a medicament recognized as effective to treat ileitis, including Crohn's disease, such as, for example,

- (a) sulfasalazine (Azulfidine EN-tabs delayed release tablets and Azulfidine tablets, Kabi Pharmacia), dosage range from 1 gram daily to 5 grams daily;
- (b) dexamethasone (Decadron, Merck & Co.), dosage range from 0.25 mg daily to 18 mg daily;
- (c) methylprednisolone acetate (Depo-Medrol, Upjohn), intra-synovial, intralesional or intramuscular dosage range from 0.5 mg daily to 50 mg daily, or weekly dosage of from 20 mg to 120 mg;
- (d) hydrocortisone (Hydrocortone, Merck & Co.), dosage range from 1 mg daily to 400 mg daily;
- (e) metronidazole (Flagyl, Searle), dosage range from 250 mg daily to 2.5 gm daily;
- (f) ebselen, intravenous, intramuscular, subcutaneous or oral dosage range from 5 mg/kg daily to 500 mg/kg daily;
- (g) sustained-release tablets of 5-aminosalicylic acid (mesalamine; (Asacol delayed-release tablets, a composition consisting of 5-aminosalicylic acid coated with Eudragit-S, an acrylic-based resin pH-dependent delayed release substance; Procter & Gamble Pharmaceuticals), dosage range from 500 mg daily to 5 grams daily;
- (h) sustained-release tablets of 5-aminosalicylic acid (Pentasa, a composition consisting of 5-aminosalicylic acid coated with a semipermeable membrane of ethyl cellulose; Ferring A/S Vanlose), dosage range from 500 mg daily to 5 gm daily;
- (i) prednisolone (Pediapred, Fisons), dosage range from 1 mg daily to 250 mg daily, or alternate day dosing;
- (j) cortisone (Cortone, Merck & Co.), dosage range from 5 mg

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daily to 400 mg daily;

(k) prednisone (Deltasone, Upjohn), dosage range from 1 mg daily to 250 mg daily, or alternate day dosing;

(l) methylprednisolone (Medrol, Upjohn), dosage range from 1 mg daily to 250 mg daily, or alternate day dosing;

(m) triamcinolone (Aristocort, Fujisawa), dosage range from 1 mg daily to 200 mg daily, or alternate day dosing;

(n) triamcinolone diacetate (Aristocort suspensions, Fujisawa), intramuscular, intrasynovial or intralesional dosage range from 1 mg daily to 200 mg daily, or alternate day dosing;

(o) betamethasone (Celestone, Schering), dosage range from 0.2 mg daily to 12 mg daily, or alternate day dosing;

(p) betamethasone (Celestone Soluspan suspension, Schering), intramuscular or intralesional dosage range from 0.1 mg daily to 10 mg daily, or alternate day dosing;

(q) dexamethasone (Decadron phosphate injection, Merck & Co.), intramuscular, intravenous or intralesional dosage range from 0.1 mg daily to 10 mg daily;

(r) cortisone (Cortone suspension, Merck & Co.), intramuscular dosage range from 5 mg daily to 400 mg daily;

(s) hydrocortisone (Hydrocortone phosphate injection, Merck & Co.), intramuscular, intravenous or subcutaneous dosage range from 1 mg daily to 400 mg daily;

(t) prednisolone (Hydeltrasol injection, Merck & Co.), intravenous, intramuscular, intra-articular, intralesional and soft tissue dosage range from 1 mg daily to 100 mg daily;

(u) diphenoxylate, dosage range from 2.5 mg daily to 20 mg daily;

(v) diphenoxylate in combination with atropine sulfate (Lomotil, Searle), dosage range from 2.5 mg diphenoxylate and 25 µg atropine sulfate daily to 20 mg diphenoxylate and 200 µg atropine sulfate daily;

(w) deodorized opium tincture, dosage range from 0.5 ml daily to 3 ml daily;

(x) codeine, dosage range from 1 mg daily to 150 mg daily;

(y) azathioprine (Imuran, Burroughs Wellcome), dosage range

from 0.1 mg/kg daily to 2.5 mg/kg daily;

(z) 6-mercaptopurine (*Purinethol*, Burroughs Wellcome), dosage range from 0.1 mg/kg daily to 2.5 mg/kg daily;

(a') cyclosporin A (*Sandimmune*, Sandoz Pharmaceutical), dosage range from 1 mg/kg daily to 15 mg/kg daily;

(b') methotrexate (*Lederle*), dosage range from 2.5 mg daily to 30 mg daily, or doses from 5 mg to 50 mg once or twice weekly; and

(c') methotrexate sodium (*Methotrexate LPF*, Lederle), intramuscular, intravenous, intra-arterial or intrathecal dosage range from 2.5 mg daily to 30 mg daily, or doses from 5 mg to 50 mg once or twice weekly.

The following illustrate specific formulations according to the present invention.

trans-4-aminocyclohexane-

carboxylic acid	1 gm
α -tocopherol	500 I.U.
prednisolone	5 mg

<i>p</i> -aminobenzoic acid	15 gm
potassium citrate monohydrate	15 gm
diphenoxylate	20 mg

5-amino-2-methoxybenzoic acid	5 gm
butylated-hydroxytoluene	500 mg
dihydrolipoic acid	250 mg
ebselen	5 gm

Example 4

Clinical treatment of ulcerative colitis, a form of inflammatory bowel disease can be improved by use of a composition comprising from about 1 gm to about 20 gm of at least one primary therapeutic agent comprising a primary amine benzoic acid derivative having a molecular weight of from about 100 to about 1,400 Daltons, and optionally at least one substance selected from those noted above in section (v) through section (ix), and a medicament recognized as effective to treat ulcerative colitis, a form of inflammatory bowel

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disease, such as, for example,

(a) sulfasalazine (Azulfidine *EN-tabs* delayed release tablets and Azulfidine tablets, Kabi Pharmacia), dosage range from 1 gm daily to 5 gm daily;

(b) 5-aminosalicylic acid, oral or intrarectal dosage range from 10 mg/kg to 500 mg/kg;

(c) 7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid, oral or intra-rectal dosage range from 0.1 mg/kg to 80 mg/kg;

(d) glutathione, intrarectal dosage range from 1 mg/kg to 20 mg/kg;

(e) zileuton, dosage range from 100 mg daily to 1 gram daily;

(f) olsalazine (*Dipentum*, Pharmacia Ltd.), dosage range from 200 mg daily to 2 gm daily;

(g) disodium azodisalicylate, dosage range from 200 mg daily to 4 gm daily;

(h) dexamethasone (*Decadron*, Merck & Co.), dosage range from 0.25 mg daily to 18 mg daily;

(i) eicosapentaenoic acid (or commercial products containing this substance as the active ingredient, including *MaxEPA* capsules, 18 gm of which contains 3.2 gm eicosapentaenoic acid), dosage range from 500 mg daily to 10 gm daily;

(j) salicylsulfapyridine (*Salazopyrin*, Pharmacia AB), dosage range from 1 gm daily to 5 gm daily;

(k) sustained-release tablets of 5-aminosalicylic acid (*Pentasa*, a composition consisting of 5-aminosalicylic acid coated with a semipermeable membrane of ethyl cellulose; *Ferring A/S Vanlose*), dosage range from 500 mg daily to 5 gm daily;

(l) sustained-release tablets of 5-aminosalicylic acid (mesalamine; *Asacol* delayed-release tablets, a composition consisting of 5-aminosalicylic acid coated with Eudragit-S, an acrylic-based resin pH-dependent delayed release substance; *Procter & Gamble Pharmaceuticals*), dosage range from 500 mg daily to 5 gm daily;

(m) diazo sulfanilamide ethylene polymer of 5-aminosalicylic acid, dosage range from 500 mg daily to 5 gm daily;

(n) hydrocortisone (*Hydrocortone*, Merck & Co.), dosage range from 1 mg daily to 400 mg daily;

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- (o) prednisolone (Pediapred, Fisons), dosage range from 1 mg daily or every other day to 250 mg daily;
 - (p) cortisone (Cortone, Merck & Co.), dosage range from 5 mg daily to 400 mg daily;
 - (q) prednisone (Deltasone, Upjohn), dosage range from 1 mg daily to 250 mg daily, or alternate day dosing;
 - (r) methylprednisolone (Medrol, Upjohn), dosage range from 1 mg daily to 250 mg daily, or alternate day dosing;
 - (s) methylprednisolone acetate (Depo-Medrol, Upjohn), intra-synovial, intralesional or intramuscular dosage range from 0.5 mg daily to 50 mg daily, or weekly dosage of from 20 mg to 120 mg;
 - (t) triamcinolone (Aristocort, Fujisawa), dosage range from 1 mg daily to 200 mg daily, or alternate day dosing;
 - (u) triamcinolone diacetate (Aristocort suspensions, Fujisawa), intramuscular, intrasynovial or intralesional dosage range from 1 mg daily to 200 mg daily, or alternate day dosing;
 - (v) betamethasone (Celestone, Schering), dosage range from 0.2 mg daily to 12 mg daily, or alternate day dosing;
 - (w) betamethasone (Celestone Soluspan suspension, Schering), intramuscular or intralesional dosage range from 0.1 mg daily to 10 mg daily, or alternate day dosing;
 - (x) dexamethasone (Decadron phosphate injection, Merck & Co.), intramuscular, intravenous or intralesional dosage range from 0.1 mg daily to 10 mg daily;
 - (y) cortisone (Cortone suspension, Merck & Co.), intramuscular dosage range from 5 mg daily to 400 mg daily;
 - (z) hydrocortisone (Hydrocortone phosphate injection, Merck & Co.), intramuscular, intravenous or subcutaneous dosage range from 1 mg daily to 400 mg daily;
 - (a') prednisolone (Hydeltrasol injection, Merck & Co.), intravenous, intramuscular, intra-articular, intralesional and soft tissue dosage range from 1 mg daily to 100 mg daily;
 - (b') azathioprine (Imuran, Burroughs Wellcome), dosage range from 0.1 mg/kg daily to 2.5 mg/kg daily;
 - (c') 6-mercaptopurine (Purinethol, Burroughs Wellcome), dosage range from 0.1 mg/kg daily to 2.5 mg/kg daily;
 - (d') diphenoxylate, dosage range from 2.5 mg daily to 20 mg

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daily;

(e') diphenoxylate in combination with atropine sulfate (Lomotil, Searle), dosage range from 2.5 mg diphenoxylate and 25 µg atropine sulfate daily to 20 mg diphenoxylate and 200 µg atropine sulfate daily;

(f') deodorized opium tincture, dosage range from 0.5 ml daily to 3 ml daily;

(g') codeine, dosage range from 1 mg daily to 150 mg daily;

(h') loperamide (Imodium, Janssen Pharmaceutica), dosage range from 2 mg daily to 16 mg daily;

(i') corticotropin (ACTH), intravenous dosage range from 25 units daily to 150 units daily;

(j') cyclosporin A (Sandimmune, Sandoz Pharmaceutical), dosage range from 1 mg/kg daily to 15 mg/kg daily;

(k') benztropine mesylate (Cogentin, Merck & Co.), dosage range from 0.5 mg daily to 10 mg daily;

(l') trihexyphenidyl (Artane, Lederle), dosage range from 2 mg daily to 20 mg daily;

(m') procyclidine (Kemadrin, Burroughs Wellcome), dosage range from 2 mg daily to 50 mg daily;

(n') biperiden (Akineton, Knoll Pharmaceuticals), dosage range from 0.5 mg daily to 10 mg daily;

(o') ethopropazine, dosage range from 10 mg daily to 500 mg daily;

(p') scopolamine, dosage range from 0.1 mg daily to 1 mg daily;

(q') benztropine mesylate (Cogentin injection, Merck & Co.), intravenous, intramuscular or subcutaneous dosage range from 0.5 mg daily to 10 mg daily;

(r') biperiden lactate (parenteral Akineton, Knoll Pharmaceuticals), intravenous, intramuscular or subcutaneous dosage range from 0.5 mg daily to 10 mg daily;

(s') propantheline bromide (Pro-Banthine, Schiapparelli Searle), dosage range from 7.5 mg daily to 120 mg daily; and

(t') oxybutynin chloride (Ditropan, Marion Merrell Dow), dosage range from 5 mg daily to 20 mg daily.

The following illustrate specific formulations according to the present invention.

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p-aminobenzoic acid	1 gm
N-acetylcysteine	1 gm
zileuton	100 mg
p-aminobenzoic acid, potassium salt	20 gm
d- α -tocopheryl succinate	2,000 I.U.
dexamethasone	10 mg
4-guanidinobenzoic acid HCl	5 gm
prostaglandin B ₁ oligomers	5 gm
acetylhomocysteine thiolactone	1 gm
trihexyphenidyl	10 mg

Example 5

Clinical treatment of interstitial cystitis can be improved by use of a composition comprising from about 1 gm to about 20 gm of at least one primary therapeutic agent comprising a primary amine benzoic acid derivative having a molecular weight of from about 100 to about 1,400 Daltons, and optionally at least one substance selected from those noted above in section (v) through section (ix), and a medicament recognized as effective to treat interstitial cystitis, such as, for example,

(a) propantheline bromide (Pro-Banthine, Schiapparelli Searle), dosage range from 7.5 mg daily to 120 mg daily;

(b) oxybutynin chloride (Ditropan, Marion Merrell Dow), dosage range from 5 mg daily to 20 mg daily;

(c) benztropine mesylate (Cogentin, Merck & Co.), dosage range from 0.5 mg daily to 10 mg daily;

(d) trihexyphenidyl (Artane, Lederle), dosage range from 2 mg daily to 20 mg daily;

(e) procyclidine (Kemadrin, Burroughs Wellcome), dosage range from 2 mg daily to 50 mg daily;

(f) biperiden (Akineton, Knoll Pharmaceuticals), dosage range from 0.5 mg daily to 10 mg daily;

(g) ethopropazine, dosage range from 10 mg daily to 500 mg daily;

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(h) scopolamine, dosage range from 0.1 mg daily to 1 mg daily;

(i) benztropine mesylate (Cogentin injection, Merck & Co.), intravenous, intramuscular or subcutaneous dosage range from 0.5 mg daily to 10 mg daily; and

(j) biperiden lactate (parenteral Akineton, Knoll Pharmaceuticals), intravenous, intramuscular or subcutaneous dosage range from 0.5 mg daily to 10 mg daily.

The following illustrate specific formulations according to the present invention.

p-aminobenzoic acid	1 gm
d- α -tocopheryl succinate	500 I.U.
benztropine mesylate	1 mg
p-aminobenzoic acid, potassium salt	20 gm
mixed tocopherols	3,500 I.U.
N-acetylcysteine	10 gm
oxybutynin chloride	20 mg
o-aminomethylbenzoic acid	5 gm
α -tocopherol nicotinate	1,500 I.U.
dihydrolipoic acid	250 mg
ethopropazine	200 mg

Example 6

Clinical treatment of psoriasis can be improved by use of a composition, administered in various oral, topical, intravenous, intramuscular, subcutaneous and intralesional combinations, comprising from about 1 gm to about 20 gm of at least one primary therapeutic agent comprising a primary amine benzoic acid derivative having a molecular weight of from about 100 to about 1,400 Daltons, and optionally at least one substance selected from those noted above in section (v) through section (ix), and a medicament recognized as effective to treat psoriasis, such as, for example,

(a) 7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid, dosage range from 0.1 mg/kg daily to 80 mg/kg daily;

- (b) eicosapentaenoic acid, dosage range from 1 gm daily to 5 gm daily;
- (c) dexamethasone (Decadron, Merck & Co.), dosage range from 0.25 mg daily to 18 mg daily;
- (d) methotrexate (Rheumatrex, Lederle Laboratories), dosage range from 1 mg weekly to 20 mg weekly;
- (e) hydrocortisone (Hydrocortone, Merck & Co.), dosage range from 1 mg daily to 400 mg daily;
- (f) prednisolone (Pediapred, Fisons), dosage range from 1 mg daily or every other day to 250 mg daily;
- (g) cortisone (Cortone, Merck & Co.), dosage range from 5 mg daily to 400 mg daily;
- (h) prednisone (Deltasone, Upjohn), dosage range from 1 mg daily to 250 mg daily, or alternate day dosing;
- (i) methylprednisolone (Medrol, Upjohn), dosage range from 1 mg daily to 250 mg daily, or alternate day dosing;
- (j) methylprednisolone acetate (Depo-Medrol, Upjohn), intra-synovial, intralesional or intramuscular dosage range from 0.5 mg daily to 50 mg daily, or weekly dosage of from 20 mg to 120 mg;
- (k) triamcinolone (Aristocort, Fujisawa), dosage range from 1 mg daily to 200 mg daily, or alternate day dosing;
- (l) triamcinolone diacetate (Aristocort suspensions, Fujisawa), intramuscular, intrasynovial or intralesional dosage range from 1 mg daily to 200 mg daily, or alternate day dosing;
- (m) betamethasone (Celestone, Schering), dosage range from 0.2 mg daily to 12 mg daily, or alternate day dosing;
- (n) betamethasone (Celestone Soluspan suspension, Schering), intramuscular or intralesional dosage range from 0.1 mg daily to 10 mg daily, or alternate day dosing;
- (o) dexamethasone (Decadron phosphate injection, Merck & Co.), intramuscular, intravenous or intralesional dosage range from 0.1 mg daily to 10 mg daily;
- (p) cortisone (Cortone suspension, Merck & Co.), intramuscular dosage range from 5 mg daily to 400 mg daily;
- (q) hydrocortisone (Hydrocortone phosphate injection, Merck & Co.), intramuscular, intravenous or subcutaneous dosage range from 1 mg daily to 400 mg daily;

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(r) hydrocortisone (*Hydrocortone acetate suspension*, Merck & Co.), intra-articular, intralesional or soft tissue injection dosage range from 1 mg daily to 400 mg daily;

(s) prednisolone (*Hydeltrasol injection*, Merck & Co.), intravenous, intramuscular, intra-articular, intralesional and soft tissue dosage range from 1 mg daily to 100 mg daily;

(t) triamcinolone acetonide (*Aristocort A topical cream*, Fujisawa), dosage range of from one to four applications per day to affected skin areas;

(u) alclometasone 17,21-dipropionate (*Aclovate*, Glaxo Dermatology), dosage range of from one to three applications per day;

(v) hydrocortisone (*Anusol-HC*, Parke-Davis), dosage range of from one to four applications per day;

(w) fluticasone propionate (*Cutivate cream*, Glaxo Dermatology), dosage range of from one to three applications per day;

(x) betamethasone 17,21-dipropionate (*Diprolene*, Schering), dosage range of from one to three applications per day;

(y) mometasone 17-(2-furoate) (*Elocon*, Schering), dosage range of from once weekly to once daily;

(z) clobetasol propionate (*Temovate*, Glaxo Dermatology), dosage range of from one to three applications per day;

(a') 0.05% coal tar topical composition (*DHS Tar Gel Shampoo*, Person & Covey), dosage range of from one use per day to one use per week;

(b') 12.5% coal tar topical composition (*Denorex Extra Strength Shampoo*, Whitehall Laboratories), dosage range of from one use per day to one use per week;

(c') methoxsalen (*Oxsoralen lotion*, 1%, ICN), dosage range from a topical application plus ultraviolet light exposure once per month to applications plus ultraviolet light exposure three times per week;

(d') methoxsalen (*Oxsoralen-Ultra capsules*, ICN), dosage range from one 10 mg capsule plus ultraviolet light exposure once per month to two 10 mg capsules plus ultraviolet light

exposure three times per week; ⁵⁹
 (e') etretinate (Tegison, Roche Dermatologics), dosage range from 0.125 mg/kg daily to 1.5 mg/kg daily;
 (f') isotretinoin (Accutane, Roche Dermatologics), dosage range from 0.1 mg/kg daily to 2 mg/kg daily;
 (g') anthralin (Drithocrema topical creams, American Dermal), dosage range of from one application per week to one application per day for each concentration of drug, ranging from 0.1% to 1%;
 (h') cyclosporin A (Sandimmune, Sandoz Pharmaceutical), dosage range from 1 mg/kg daily to 15 mg/kg daily;
 (i') vitamin D₃, 0.001% to 0.5 % in cream, lotion or gel base, topical application from once weekly to four times daily; and
 (j') salicylic acid, 0.001% to 0.5 % in cream, lotion or gel base, topical application from once weekly to four times daily.

The following illustrate specific formulations according to the present invention.

4-(aminoguanidino)benzoic acid	1 gm
nordihydroguaiaretic acid	7.5 gm
methylprednisolone	2.5 mg

p-aminophenylacetic acid	20 gm
probucol	1 gm
etretinate	100 mg

p-aminobenzoic acid	5 gm
timonacic	250 mg
cyclosporin A	500 mg

Example 7

Clinical treatment of rheumatoid arthritis can be improved by use of a composition comprising from about 1 gm to about 20 gm of at least one primary therapeutic agent comprising a primary amine benzoic acid derivative having a molecular weight of from about 100 to about 1,400 Daltons, and optionally at least one substance selected from those noted above in

section (v) through section (ix)⁴⁰, and a medicament recognized as effective to treat rheumatoid arthritis, such as, for example,

- (a) meclofenamate (Meclofen), dosage range from 100 mg daily to 800 mg daily;
- (b) mefenamic acid (Ponstel), dosage range from 200 mg daily to 1.5 gm daily;
- (c) flufenamic acid, dosage range from 100 mg daily to 1 gm daily;
- (d) amfenac, dosage range from 1 μ g/kg daily to 1 mg/kg daily;
- (e) ethyl 2-amino-3-benzoylphenylacetate, dosage range from 10 μ g/kg daily to 10 mg/kg daily;
- (f) diclofenac (Voltaren), dosage range from 10 mg daily to 200 mg daily;
- (g) etodolac (Lodine, Wyeth-Ayerst Laboratories), dosage range from 200 mg daily to 2 gm daily;
- (h) metiazinic acid, dosage range from 1 mg/kg daily to 100 mg/kg daily;
- (i) indomethacin (Indocin), dosage range from 25 mg daily to 250 mg daily;
- (j) fenclozic acid, dosage range from 25 mg daily to 500 mg daily;
- (k) isofezolac, dosage range from 0.1 mg/kg daily to 25 mg/kg daily;
- (l) sulindac (Clinoril, Merck & Co.), dosage range from 50 mg daily to 500 mg daily;
- (m) tolmetin (Tolectin), dosage range from 100 mg daily to 2 gm daily;
- (n) glucametacin, dosage range from 50 mg daily to 600 mg daily;
- (o) cinmetacin, dosage range from 2 mg/kg daily to 400 mg/kg daily;
- (p) fenclofenac, dosage range from 200 mg daily to 2 gm daily;
- (q) fenbufen, dosage range from 250 mg daily to 1.25 gm daily;
- (r) butibufen, dosage range from 40 mg/kg daily to 400 mg/kg daily;

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- (s) ketorolac tromethamine (Toradol, Syntex), dosage range from 5 mg daily to 150 mg daily;
 - (t) tinoridine, dosage range from 2.5 mg/kg daily to 250 mg/kg daily;
 - (u) fenoprofen (Nalfon), dosage range from 250 mg daily to 3.2 gm daily;
 - (v) flurbiprofen (Ansaid), dosage range from 50 mg daily to 500 mg daily;
 - (w) ibuprofen (Motrin), dosage range from 200 mg daily to 3.2 gm daily;
 - (x) ketoprofen (Orudis), dosage range from 25 mg daily to 500 mg daily;
 - (y) naproxen (Naprosyn), dosage range from 125 mg daily to 1.25 gm daily;
 - (z) bucloxic acid, dosage range from 200 mg daily to 2 gm daily;
 - (a') the (S) (+) enantiomer of carprofen, dosage range from 10 mg daily to 750 mg daily;
 - (b') phenylbutazone (Azolid), dosage range from 2 mg/kg daily to 100 mg/kg daily;
 - (c') oxyphenbutazone (Taneril), dosage range from 100 mg daily to 1 gm daily;
 - (d') feprazone, dosage range from 100 mg daily to 1.5 gm daily;
 - (e') imidazole salicylate, dosage range from 50 μ mol/kg daily to 0.5 mmol/kg daily;
 - (f') diflunisal, dosage range from 250 mg daily to 1.5 gm daily;
 - (g') sulfasalazine, dosage range from 200 mg daily to 3 gm daily;
 - (h') benorylate, dosage range from 1 gm daily to 7 gm daily;
 - (i') piroxicam (Feldene), dosage range from 5 mg daily to 25 mg daily;
 - (j') isoxicam, dosage range from 50 mg daily to 500 mg daily;
 - (k') auranofin (Ridaura, SmithKline Beecham), dosage range from 1 mg daily to 9 mg daily;
 - (l') aurothioglucose (Solganal, Schering), intramuscular dosage range from 1 mg weekly to 40 mg weekly;
 - (m') gold sodium thiomalate (Myochryisine, Merck & Co.),

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intramuscular dosage range from 1 mg weekly to 50 mg weekly;
(n') hydroxychloroquine (Plaquenil, Sanofi Winthrop Pharmaceuticals), dosage range from 50 mg (equivalent to 39 mg base) daily to 600 mg (equivalent to 465 mg base) daily;
(o') chloroquine, dosage range from 50 mg daily to 500 mg daily;
(p') methotrexate (Rheumatrex, Lederle Laboratories), dosage range from 1 mg weekly to 20 mg weekly;
(q') D-penicillamine (Cuprimine, Merck & Co.), dosage range from 25 mg daily to 1.5 grams daily;
(r') cyclophosphamide (Cytosan, Bristol-Myers Oncology), dosage range from 0.1 mg/kg daily to 5 mg/kg daily;
(s') prednisone (Deltasone, Upjohn), dosage range from 1 mg daily to 250 mg daily, or alternate day dosing;
(t') dexamethasone (Decadron, Merck & Co.), dosage range from 0.25 mg daily to 18 mg daily;
(u') methylprednisolone (Medrol, Upjohn), dosage range from 1 mg daily to 250 mg daily, or alternate day dosing;
(v') (10-methoxy-4H-benzo[4,5]cyclohepta-[1,2-b]-thiophene-4-yliden)acetic acid, dosage range from 0.5 mg/kg daily to 100 mg/kg daily;
(w') cyclosporin A (Sandimmune, Sandoz Pharmaceutical), dosage range from 1 mg/kg daily to 250 mg/kg daily or three times weekly;
(x') neutral macrolide of molecular formula $C_{44}H_{69}NO_{12} \cdot H_2O$ derived from Streptomyces tsukubaensis No. 9993 (FK506), dosage range from 0.5 mg/kg daily to 50 mg/kg daily;
(y') rapamycin, dosage range from 1 mg/kg daily to 250 mg/kg daily or three times weekly;
(z') azathioprine (Imuran, Burroughs Wellcome), oral or intravenous dosage range from 75 μ g/kg daily to 2.5 mg/kg daily;
(a'') nabumetone (Relafen, SmithKline Beecham), dosage range from 200 mg daily to 2 gm daily;
(b'') eicosapentaenoic acid, dosage range from 500 mg daily to 10 gm daily;
(c'') aloxiprin, dosage range from 1 gm daily to 7 gm daily;
(d'') azapropazone, dosage range from 500 mg daily to 5 gm daily;
(e'') amiprilose, dosage range from 1 gm daily to 8 gm daily;

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- (f'') chlorambucil (*Leukeran*, Burroughs Wellcome), dosage range from 0.5 mg daily to 10 mg daily;
- (g'') aceclofenac, dosage range from 0.2 mg/kg daily to 10 mg/kg daily;
- (h'') apocynin, dosage range from 1 mg/kg daily to 100 mg/kg daily;
- (i'') capsaicin, intravenous, intramuscular, subcutaneous or oral dosage range from 5 mg/kg daily to 200 mg/kg daily;
- (j'') 6-(2,4-difluorophenoxy)-5-methylsulfonylamino-1-indanone (Ciba-Geigy AG), dosage range from 0.2 mg/kg daily to 20 mg/kg daily;
- (k'') dapson, dosage range from 20 mg daily to 200 mg daily;
- (l'') solubilized chicken type II collagen, dosage range from 50 µg daily to 20 mg daily;
- (m'') 15-deoxyspergualin, intravenous, intramuscular, subcutaneous or oral dosage range from 0.5 mg/kg daily to 10 mg/kg daily;
- (n'') diacetyl-splenopentin, intravenous, intramuscular or subcutaneous dosage range from 100 µg/kg daily to 3 mg/kg daily;
- (o'') diaveridine, dosage range from 25 mg/kg daily to 500 mg/kg daily;
- (p'') ditazol, dosage range from 25 mg/kg daily to 750 mg daily;
- (q'') droxicam, dosage range from 0.1 mg/kg daily to 50 mg/kg daily;
- (r'') (Z)-3-[4-(acetyloxy)-5-ethyl-3-methoxy-1-naphthalenyl]-2-methyl-2-propenoic acid, dosage range from 10 mg/kg daily to 500 mg/kg daily;
- (s'') ebselen, intravenous, intramuscular, subcutaneous or oral dosage range from 5 mg/kg daily to 500 mg/kg daily;
- (t'') 1-p-chlorobenzyl-2-dimethyl-amino-methylcyclohexen-1,2, dosage range from 2.5 mg/kg daily to 250 mg/kg daily;
- (u'') etoclofene, intravenous, intramuscular, subcutaneous or oral dosage range from 1 mg/kg daily to 400 mg/kg daily;
- (v'') felbinac, dosage range from 100 mg daily to 1.25 gm daily;
- (w'') fenclorac, dosage range from 0.5 mg/kg daily to 50 mg/kg daily;

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- (x'') fenclozic acid, dosage range from 2.5 mg/kg daily to 250 mg/kg daily;
- (y'') fendosal, dosage range from 5 mg/kg daily to 200 mg/kg daily;
- (z'') isoxepac, dosage range from 200 mg daily to 2 gm daily;
- (a''') leflunomide, dosage range from 50 µg daily to 50 mg daily;
- (b''') lobenzarit, dosage range from 50 mg daily to 750 mg daily;
- (c''') lonazolac-Ca, dosage range from 100 mg daily to 1 gm daily;
- (d''') 5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-3-(dimethylamino)-4-thiazolidinone, dosage range from 1 mg/kg daily to 100 mg/kg daily;
- (e''') 5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-3-(methylamino)-4-thiazolidinone, dosage range from 1 mg/kg daily to 100 mg/kg daily;
- (f''') bumadizon-calcium (Eumotol), dosage range from 100 mg daily to 1 gm daily;
- (g''') azapropazone, dosage range from 100 mg daily to 1 gm daily;
- (h''') D-myoinositol-1.2.6-trisphosphate, intravenous, intramuscular, subcutaneous or oral dosage range from 10 mg/kg daily to 1.5 gm daily;
- (i''') eicosapentaenoic acid (as commercial products containing this substance as the active ingredient, including MaxEPA capsules, 18 gm of which contains 3.2 gm eicosapentaenoic acid), dosage range of eicosapentaenoic acid from 500 mg daily to 10 gm daily;
- (j''') ibufenac, dosage range from 1 mg/kg daily to 100 mg/kg daily;
- (k''') nimesulide, dosage range from 100 mg daily to 2 gm daily;
- (l''') oxametacine, dosage range from 50 mg daily to 500 mg daily;
- (m''') oxaprozin, dosage range from 150 mg daily to 1.5 gm daily;
- (n''') suxibuzone, dosage range from 2 mg/kg daily to 150 mg/kg daily;

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- (o''') pirprofen, dosage range from 100 mg daily to 1.5 gm daily;
- (p''') proquazone, dosage range from 150 mg daily to 1.5 gm daily;
- (q''') triamcinolone acetonide, intravenous, intramuscular, subcutaneous or oral dosage range from 5 μ g/kg daily to 0.1 mg/kg daily;
- (r''') suprofen; dosage range from 5 mg/kg daily to 100 mg/kg daily;
- (s''') tenoxicam, dosage range from 5 mg daily to 40 mg daily;
- (t''') tiaprofenic acid, dosage range from 100 mg daily to 1 gm daily;
- (u''') tolfenamic acid, dosage range from 100 mg daily to 600 mg daily;
- (v''') difenpiramide, dosage range from 250 mg daily to 1.5 gm daily;
- (w''') isofezolac, dosage range from 0.5 mg/kg daily to 50 mg/kg daily;
- (x''') tiopronin, intravenous, intramuscular, subcutaneous or oral dosage range from 5 mg/kg daily to 100 mg/kg daily;
- (y''') 5-thiopyridoxine, dosage range from 50 mg daily to 2 gm daily;
- (z''') hydrocortisone (Hydrocortone, Merck & Co.), dosage range from 1 mg daily to 400 mg daily;
- (a''') prednisolone (Pediapred, Fisons), dosage range from 1 mg daily or every other day to 250 mg daily;
- (b''') cortisone (Cortone, Merck & Co.), dosage range from 5 mg daily to 400 mg daily;
- (c''') methylprednisolone acetate (Depo-Medrol, Upjohn), intrasynovial, intralesional or intramuscular dosage range from 0.5 mg daily to 50 mg daily, or weekly dosage of from 20 mg to 120 mg;
- (d''') triamcinolone (Aristocort, Fujisawa), dosage range from 1 mg daily to 200 mg daily, or alternate day dosing;
- (e''') triamcinolone diacetate (Aristocort suspensions, Fujisawa), intramuscular, intrasynovial or intralesional dosage range from 1 mg daily to 200 mg daily, or alternate day dosing;
- (f''') betamethasone (Celestone, Schering), dosage range from

0.2 mg daily to 12 mg daily, or alternate day dosing;
(g''') betamethasone (Celestone Soluspan suspension, Schering), intramuscular or intralesional dosage range from 0.1 mg daily to 10 mg daily, or alternate day dosing;
(h''') dexamethasone (Decadron phosphate injection, Merck & Co.), intramuscular, intravenous or intralesional dosage range from 0.1 mg daily to 10 mg daily;
(i''') cortisone (Cortone suspension, Merck & Co.), intramuscular dosage range from 5 mg daily to 400 mg daily;
(j''') hydrocortisone (Hydrocortone phosphate injection, Merck & Co.), intramuscular, intravenous or subcutaneous dosage range from 1 mg daily to 400 mg daily;
(k''') hydrocortisone (Hydrocortone acetate suspension, Merck & Co.), intra-articular, intralesional or soft tissue injection dosage range from 1 mg daily to 400 mg daily;
(l''') prednisolone (Hydeltrasol injection, Merck & Co.), intravenous, intramuscular, intra-articular, intralesional and

soft tissue dosage range from 1 mg daily to 100 mg daily;
(m''') aspirin, dosage range from 300 mg daily to 6.5 gm daily;
(n''') calcium acetylsalicylate, dosage range from 300 mg daily to 6.5 gm daily;
(o''') choline salicylate, dosage range from 500 mg daily to 4 gm daily;
(p''') choline magnesium trisalicylate (Trilisate, Purdue Frederick), dosage range from 500 mg daily to 4 gm daily;
(q''') magnesium salicylate, dosage range from 500 mg daily to 4 gm daily;
(r''') salsalate (Salflex, Carnrick Laboratories), dosage range from 500 mg daily to 4 gm daily;
(s''') sulfasalazine (Azulfidine EN-tabs delayed release tablets and Azulfidine tablets, Kabi Pharmacia), dosage range from 1 gm daily to 5 gm daily;
(t''') cyclophosphamide (Cytoxan for injection, Bristol-Myers Oncology), dosage range from 0.1 mg/kg daily to 5 mg/kg daily, 2 mg/kg to 5 mg/kg twice weekly or 10 mg/kg to 15 mg/kg every seven to ten days;
(u''') N,N'-diphenyl-p-phenylenediamine, dosage range from 10

mg/kg daily to 250 mg/kg daily;⁶²

(v''') tenidap (Pfizer), dosage range from 25 mg daily to 2 gm daily;

(w''') ketorolac tromethamine (Toradol IM, Syntex), intramuscular dosage range from 5 mg daily to 150 mg daily; and

(x''') carprofen, dosage range from 0.2 mg/kg daily to 50 mg/kg daily;

The following illustrate specific formulations according to the present invention.

4-guanidinobenzoic acid HCl	1 gm
mixed tocopherols	500 I.U.
prednisone	5 mg

p-aminobenzoic acid	20 gm
d- α -tocopheryl succinate	3,500 I.U.
L-methionine	2 gm
sulindac	500 mg

4-(aminoguanidino)benzoic acid	5 gm
acetylhomocysteine thiolactone	1 gm
azathioprine	75 mg

Example 8

Clinical treatment of ankylosing spondylitis can be improved by use of a composition comprising from about 1 gm to about 20 gm of at least one primary therapeutic agent comprising a primary amine benzoic acid derivative having a molecular weight of from about 100 to about 1,400 Daltons, and optionally at least one substance selected from those noted above in section (v) through section (ix), and a medicament recognized as effective to treat ankylosing spondylitis, such as, for example,

- (a) isoxicam, dosage range from 25 mg daily to 400 mg daily;
- (b) ketoprofen, dosage range from 50 mg daily to 500 mg daily;
- (c) diclofenac, dosage range from 25 mg daily to 500 mg daily;

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- (d) fenclofenac, dosage range from 150 mg daily to 1.5 gm daily;
- (e) phenylbutazone, dosage range from 50 mg daily to 400 mg daily;
- (f) prenazone, dosage range from 1 mg/kg daily to 100 mg/kg daily;
- (g) nabumetone, dosage range from 200 mg daily to 2 gm daily;
- (h) indomethacin, dosage range from 50 mg daily to 500 mg daily;
- (i) sulindac (Clinoril, Merck & Co.), dosage range from 50 mg daily to 500 mg daily;
- (j) carprofen, dosage range from 25 mg daily to 300 mg daily;
- (k) dexamethasone (Decadron, Merck & Co.), dosage range from 0.25 mg daily to 18 mg daily;
- (l) proquazone, dosage range from 150 mg daily to 1.5 gm daily;
- (m) ibuprofen, dosage range from 200 mg daily to 2 gm daily;
- (n) tenoxicam, dosage range from 5 mg daily to 50 mg daily;
- (o) piroxicam, dosage range from 5 mg daily to 50 mg daily;
- (p) tiaprofenic acid, dosage range from 100 mg daily to 1 gm daily;
- (q) tolfenamic acid, dosage range from 100 mg daily to 1 gm daily;
- (r) piroprofen, dosage range from 150 mg daily to 1.5 gm daily;
- (s) hydrocortisone (Hydrocortone, Merck & Co.), dosage range from 1 mg daily to 400 mg daily;
- (t) prednisolone (Pediapred, Fisons), dosage range from 1 mg daily or every other day to 250 mg daily;
- (u) cortisone (Cortone, Merck & Co.), dosage range from 5 mg daily to 400 mg daily;
- (v) prednisone (Deltasone, Upjohn), dosage range from 1 mg daily to 250 mg daily, or alternate day dosing;
- (w) methylprednisolone (Medrol, Upjohn), dosage range from 1 mg daily to 250 mg daily, or alternate day dosing;
- (x) methylprednisolone acetate (Depo-Medrol, Upjohn), intra-synovial, intralesional or intramuscular dosage range from 0.5 mg daily to 50 mg daily, or weekly dosage of from 20 mg to 120 mg;

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- (y) triamcinolone (Aristocort, Fujisawa), dosage range from 1 mg daily to 200 mg daily, or alternate day dosing;
 - (z) triamcinolone diacetate (Aristocort suspensions, Fujisawa), intramuscular, intrasynovial or intralesional dosage range from 1 mg daily to 200 mg daily, or alternate day dosing;
 - (a') betamethasone (Celestone, Schering), dosage range from 0.2 mg daily to 12 mg daily, or alternate day dosing;
 - (b') betamethasone (Celestone Soluspan suspension, Schering), intramuscular or intralesional dosage range from 0.1 mg daily to 10 mg daily, or alternate day dosing;
 - (c') dexamethasone (Decadron phosphate injection, Merck & Co.), intramuscular, intravenous or intralesional dosage range from 0.1 mg daily to 10 mg daily;
 - (d') cortisone (Cortone suspension, Merck & Co.), intramuscular dosage range from 5 mg daily to 400 mg daily;
 - (e') hydrocortisone (Hydrocortone phosphate injection, Merck & Co.), intramuscular, intravenous or subcutaneous dosage range from 1 mg daily to 400 mg daily;
 - (f') prednisolone (Hydeltrasol injection, Merck & Co.), intravenous, intramuscular, intra-articular, intralesional and soft tissue dosage range from 1 mg daily to 100 mg daily;
 - (g') aspirin, dosage range from 300 mg daily to 6.5 gm daily;
 - (h') calcium acetylsalicylate, dosage range from 300 mg daily to 6.5 gm daily;
 - (i') choline salicylate, dosage range from 500 mg daily to 4 gm daily;
 - (j') choline magnesium trisalicylate (Trilisate, Purdue Frederick), dosage range from 500 mg daily to 4 gm daily;
 - (k') magnesium salicylate, dosage range from 500 mg daily to 4 gm daily;
 - (l') salsalate (Salflex, Carnrick Laboratories), dosage range from 500 mg daily to 4 gm daily;
 - (m') imidazole 2-hydroxybenzoate, dosage range from 50 μ mol/kg daily to 0.5 mmol/kg daily;
 - (n') diflunisal, dosage range from 250 mg daily to 1.5 gm daily;
 - (o') sulfasalazine, dosage range from 200 mg daily to 3 gm daily;

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(p') benorylate, dosage range from 1 gm daily to 7 gm daily;
(q') naproxen (Naprosyn), dosage range from 125 mg daily to 1.25 gm daily; and
(r') oxyphenbutazone (Taneril), dosage range from 100 mg daily to 1 gm daily.

The following illustrate specific formulations according to the present invention.

4-aminophenylacetic acid	1 gm
propyl gallate	100 mg
indomethacin	50 mg
4-(guanidino)-2-methoxybenzoic acid	15 gm
tert-butylhydroquinone	1 gm
glycine	10 gm
cortisone	400 mg
4-(aminoguanidino)benzoic acid	5 gm
homocysteine	1 gm
naproxen	500 mg

Example 9

Clinical treatment of osteoarthritis can be improved by use of a composition comprising from about 1 gm to about 20 gm of at least one primary therapeutic agent comprising a primary amine benzoic acid derivative having a molecular weight of from about 100 to about 1,400 Daltons, and optionally at least one substance selected from those noted above in section (v) through section (ix), and a medicament recognized as effective to treat osteoarthritis, such as, for example,

- (a) prednisone (Deltasone, Upjohn), dosage range from 1 mg daily to 250 mg daily, or alternate day dosing;
- (b) nabumetone (Relafen, SmithKline Beecham), dosage range from 200 mg daily to 2 grams daily;
- (c) ketoprofen (Orudis), dosage range from 25 mg daily to 500 mg daily;
- (d) phenylbutazone, dosage range from 100 mg daily to 500 mg daily;
- (e) the (S) (+) enantiomer of carprofen, dosage range from 50

mg daily to 750 mg daily;

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(f) dexamethasone (Decadron, Merck & Co.), dosage range from 0.25 mg daily to 18 mg daily;

(g) diclofenac (Voltaren), dosage range from 10 mg daily to 200 mg daily;

(h) diflunisal, dosage range from 250 mg daily to 1.5 gm daily;

(i) diphenpyramide, dosage range from 250 mg daily to 1.5 gm daily;

(j) fenbufen, dosage range from 250 mg daily to 1.25 gm daily;

(k) oxyphenbutazone (Taneril), dosage range from 100 mg daily to 1 gm daily;

(l) indomethacin (Indocin), dosage range from 25 mg daily to 250 mg daily;

(m) glucametacin, dosage range from 50 mg daily to 600 mg daily;

(n) isoxicam, dosage range from 50 mg daily to 500 mg daily;

(o) lonazolac-Ca, dosage range from 100 mg daily to 1 gm daily;

(p) S-adenosylmethionine, dosage range from 500 mg daily to 10 gm daily;

(q) bumadizon-calcium (Eumotol), dosage range from 100 mg daily to 1 gm daily;

(r) diacetylrhein, dosage range from 10 mg daily to 500 mg daily;

(s) proquazone, dosage range from 150 mg daily to 1.5 gm daily;

(t) naproxen (Naprosyn), dosage range from 0.5 mg/kg daily to 25 mg/kg daily;

(u) nimesulide, dosage range from 100 mg daily to 2 gm daily;

(v) oxametacine, dosage range from 50 mg daily to 500 mg daily;

(w) piroprofen, dosage range from 100 mg daily to 1.5 gm daily;

(x) prenazone, dosage range from 150 mg daily to 1.5 gm daily;

(y) sulindac (Clinoril, Merck & Co.), dosage range from 50 mg daily to 500 mg daily;

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(z) suprofen, dosage range from 5 mg/kg daily to 100 mg/kg daily;

(a') tenoxicam, dosage range from 5 mg daily to 40 mg daily;

(b') tiaprofenic acid, dosage range from 100 mg daily to 1 gm daily;

(c') hydrocortisone (Hydrocortone, Merck & Co.), dosage range from 1 mg daily to 400 mg daily;

(d') prednisolone (Pediapred, Fisons), dosage range from 1 mg daily or every other day to 250 mg daily;

(e') cortisone (Cortone, Merck & Co.), dosage range from 5 mg daily to 400 mg daily;

(f') methylprednisolone (Medrol, Upjohn), dosage range from 1 mg daily to 250 mg daily, or alternate day dosing;

(g') methylprednisolone acetate (Depo-Medrol, Upjohn), intrasynovial, intralesional or intramuscular dosage range from 0.5 mg daily to 50 mg daily, or weekly dosage of from 20 mg to 120 mg;

(h') triamcinolone (Aristocort, Fujisawa), dosage range from 1 mg daily to 200 mg daily, or alternate day dosing;

(i') triamcinolone diacetate (Aristocort suspensions, Fujisawa), intramuscular, intrasynovial or intralesional dosage range from 1 mg daily to 200 mg daily, or alternate day dosing;

(j') betamethasone (Celestone, Schering), dosage range from 0.2 mg daily to 12 mg daily, or alternate day dosing;

(k') betamethasone (Celestone Soluspan suspension, Schering), intramuscular or intralesional dosage range from 0.1 mg daily to 10 mg daily, or alternate day dosing;

(l') dexamethasone (Decadron phosphate injection, Merck & Co.), intramuscular, intravenous or intralesional dosage range from 0.1 mg daily to 10 mg daily;

(m') cortisone (Cortone suspension, Merck & Co.), intramuscular dosage range from 5 mg daily to 400 mg daily;

(n') hydrocortisone (Hydrocortone phosphate injection, Merck & Co.), intramuscular, intravenous or subcutaneous dosage range from 1 mg daily to 400 mg daily;

(o') hydrocortisone (Hydrocortone acetate suspension, Merck & Co.), intraarticular, intralesional or soft tissue injection dosage range from 1 mg daily to 400 mg daily;

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(p') prednisolone (*Hydeltrasol* injection, Merck & Co.), intravenous, intramuscular, intra-articular, intralesional and soft tissue dosage range from 1 mg daily to 100 mg daily;

(q') aspirin, dosage range from 300 mg daily to 6.5 gm daily;

(r') calcium acetylsalicylate, dosage range from 300 mg daily to 6.5 gm daily;

(s') choline salicylate, dosage range from 500 mg daily to 4 gm daily;

(t') choline magnesium trisalicylate (*Trilisate*, Purdue Frederick), dosage range from 500 mg daily to 4 gm daily;

(u') magnesium salicylate, dosage range from 500 mg daily to 4 gm daily;

(v') salsalate (*Salflex*, Carnrick Laboratories), dosage range from 500 mg daily to 4 gm daily; and

(w') etodolac (*Lodine*, Wyeth-Ayerst Laboratories), dosage range from 200 mg daily to 2 gm daily.

The following illustrate specific formulations according to the present invention.

4-amino-2-methylbenzoic acid	1 gm
N,N'-dimethylthiourea	300 mg
etodolac	200 mg

p-aminobenzoic acid	15 gm
β -carotene	300 mg
dexamethasone	10 mg

(4-aminocyclohexane)acetic acid	5 gm
D-myo-inositol-1.2.6-trisphosphate	20 gm
suprofen	3 gm

Example 10

Clinical treatment of tendinitis or tenosynovitis can be improved by use of a composition comprising from about 1 gm to about 20 gm of at least one primary therapeutic agent comprising a primary amine benzoic acid derivative having a molecular weight of from about 100 to about 1,400 Daltons, and optionally at least one substance selected from those noted above in section (v) through section (ix), and a medicament

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recognized as effective to treat tendinitis or tenosynovitis, such as, for example,

(a) the (S)(+) enantiomer of carprofen, dosage range from 50 mg daily to 750 mg daily;

(b) dexamethasone (Decadron, Merck & Co.), dosage range from 0.25 mg daily to 18 mg daily;

(c) diclofenac (Voltaren), dosage range from 10 mg daily to 200 mg daily;

(d) fenbufen, dosage range from 250 mg daily to 1.25 gm daily;

(e) nimesulide, dosage range from 100 mg daily to 2 gm daily;

(f) oxamethacin, dosage range from 50 mg daily to 500 mg daily;

(g) pirofen, dosage range from 100 mg daily to 1.5 gm daily;

(h) proquazone, dosage range from 150 mg daily to 1.5 gm daily;

(i) sulindac (Clinoril, Merck & Co.), dosage range from 50 mg daily to 500 mg daily;

(j) tenoxicam, dosage range from 5 mg daily to 40 mg daily;

(k) tiaprofenic acid, dosage range from 100 mg daily to 1 gm daily.

(l) hydrocortisone (Hydrocortone, Merck & Co.), dosage range from 1 mg daily to 400 mg daily;

(m) prednisolone (Pediapred, Fisons), dosage range from 1 mg daily or every other day to 250 mg daily;

(n) cortisone (Cortone, Merck & Co.), dosage range from 5 mg daily to 400 mg daily;

(o) prednisone (Deltasone, Upjohn), dosage range from 1 mg daily to 250 mg daily, or alternate day dosing;

(p) methylprednisolone (Medrol, Upjohn), dosage range from 1 mg daily to 250 mg daily, or alternate day dosing;

(q) methylprednisolone acetate (Depo-Medrol, Upjohn), intra-synovial, intralesional or intramuscular dosage range from 0.5 mg daily to 50 mg daily, or weekly dosage of from 20 mg to 120 mg;

(r) triamcinolone (Aristocort, Fujisawa), dosage range from 1 mg daily to 200 mg daily, or alternate day dosing;

(s) triamcinolone diacetate (Aristocort suspensions, Fuji-

sawa), intramuscular, intrasynovial or intralesional dosage range from 1 mg daily to 200 mg daily, or alternate day dosing;

(t) betamethasone (Celestone, Schering), dosage range from 0.2 mg daily to 12 mg daily, or alternate day dosing;

(u) betamethasone (Celestone Soluspan suspension, Schering), intramuscular or intralesional dosage range from 0.1 mg daily to 10 mg daily, or alternate day dosing;

(v) dexamethasone (Decadron phosphate injection, Merck & Co.), intramuscular, intravenous or intralesional dosage range from 0.1 mg daily to 10 mg daily;

(w) cortisone (Cortone suspension, Merck & Co.), intramuscular dosage range from 5 mg daily to 400 mg daily;

(x) hydrocortisone (Hydrocortone phosphate injection, Merck & Co.), intramuscular, intravenous or subcutaneous dosage range from 1 mg daily to 400 mg daily;

(y) hydrocortisone (Hydrocortone acetate suspension, Merck & Co.), intra-articular, intralesional or soft tissue injection dosage range from 1 mg daily to 400 mg daily;

(z) prednisolone (Hydeltrasol injection, Merck & Co.), intravenous, intramuscular, intra-articular, intralesional and soft tissue dosage range from 1 mg daily to 100 mg daily;

(a') dexamethasone acetate (Decadron-LA, Merck & Co.), intramuscular and local soft tissue injected dosage range from 0.1 mg daily to 10 mg daily;

(b') indomethacin (Indocin), dosage range from 25 mg daily to 250 mg daily;

(c') aspirin, dosage range from 300 mg daily to 6.5 gm daily.

(d') vitamin B₆ (pyridoxine HCl), dosage range from 10 mg daily to 1.75 gm daily;

(e') pyridoxal, dosage range from 10 mg daily to 1.75 gm daily;

(f') pyridoxal HCl, dosage range from 10 mg daily to 1.75 gm daily;

(g') pyridoxal 5-phosphate, dosage range from 10 mg daily to 1.75 gm daily;

(h') pyridoxal 5-phosphate calcium salt, dosage range from 10 mg daily to 1.75 gm daily;

(i') pyridoxamine, dosage range from 10 mg daily to 1.75 gm

daily;

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(j') pyridoxamine dihydrochloride, dosage range from 10 mg daily to 1.75 gm daily; and

(k') pyridoxamine phosphate, dosage range from 10 mg daily to 1.75 gm daily.

The following illustrate specific formulations according to the present invention.

4-amino-2-hydroxycyclohexanecarboxylic acid	1 gm
2-aminomethyl-4-tert-butyl-6-propionylphenol	1.5 gm
pyridoxine HCl	200 mg

p-aminobenzoic acid, potassium salt	20 gm
ebselen	20 gm
carprofen	1 gm

3,5-diaminobenzoic acid	5 gm
butylated hydroxyanisole	20 mg
dexamethasone acetate	5 mg

Example 11

Clinical treatment of carpal tunnel syndrome and other cumulative trauma disorders can be improved by use of a composition comprising from about 1 gm to about 20 gm of at least one primary therapeutic agent comprising a primary amine benzoic acid derivative having a molecular weight of from about 100 to about 1,400 Daltons, and optionally at least one substance selected from those noted above in section (v) through section (ix), and a medicament recognized as effective to treat carpal tunnel syndrome and other cumulative trauma disorders, such as, for example,

(a) diclofenac (Voltaren), dosage range from 10 mg daily to 200 mg daily;

(b) dexamethasone acetate (Decadron-LA, Merck & Co.), intramuscular and local soft tissue injected dosage range from 0.1 mg daily to 10 mg daily;

(c) hydrocortisone acetate (Hydrocortone suspension, Merck & Co.), intramuscular or local soft tissue injection dosage range from 1 mg daily to 400 mg daily;

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- (d) methylprednisolone acetate (Depo-Medrol, Upjohn), intramuscular or local soft tissue dosage range from 0.5 mg daily to 50 mg daily, or weekly dosage of from 20 mg to 120 mg;
- (e) vitamin B₆ (pyridoxine HCl), dosage range from 10 mg daily to 1.75 gm daily;
- (f) pyridoxal, dosage range from 10 mg daily to 1.75 gm daily;
- (g) pyridoxal HCl, dosage range from 10 mg daily to 1.75 gm daily;
- (h) pyridoxal 5-phosphate, dosage range from 10 mg daily to 1.75 gm daily;
- (i) pyridoxal 5-phosphate calcium salt, dosage range from 10 mg daily to 1.75 gm daily;
- (j) pyridoxamine, dosage range from 10 mg daily to 1.75 gm daily;
- (k) pyridoxamine dihydrochloride, dosage range from 10 mg daily to 1.75 gm daily; and
- (l) pyridoxamine phosphate, dosage range from 10 mg daily to 1.75 gm daily.

The following illustrate specific formulations according to the present invention.

4-amino-2-(methoxy)cyclohexanecarboxylic acid	1 gm
2-(2-hydroxy-4-methylphenyl)aminothiazole HCl	100 mg
pyridoxal 5-phosphate calcium salt	50 mg

p-aminophenylacetic acid, potassium salt	20 gm
d- α -tocopheryl succinate	3,000 I.U.
diclofenac	200 mg

4-amino-2-methylbenzoic acid, potassium salt	5 gm
N,N'-diphenyl-p-phenylenediamine	10 gm
hydrocortisone acetate	100 mg

Example 12

Clinical treatment of chronic discoid or systemic lupus erythematosus can be improved by use of a composition comprising from about 1 gm to about 20 gm of at least one primary therapeutic agent comprising a primary amine benzoic acid

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derivative having a molecular weight of from about 100 to about 1,400 Daltons, and optionally at least one substance selected from those noted above in section (v) through section (ix), and a medicament recognized as effective to treat chronic discoid or systemic lupus erythematosus, such as, for example,

(a) hydroxychloroquine (Plaquenil, Sanofi Winthrop Pharmaceuticals), dosage range from 50 mg (equivalent to 39 mg base) daily to 400 mg (equivalent to 310 mg base) daily;

(b) quinacrine, dosage range from 10 mg daily to 200 mg daily;

(c) chloroquine, dosage range from 50 mg daily to 750 mg daily;

(d) amodiaquine, dosage range from 10 mg daily to 500 mg daily;

(e) triquine composition tablets (each tablet consisting of 25 mg quinacrine, 65 mg chloroquine and 50 mg hydroxychloroquine), dosage range from one quarter tablet daily to two tablets daily;

(f) 15-deoxyspergualin, intravenous, intramuscular, subcutaneous or oral dosage range from 0.5 mg/kg daily to 10 mg/kg daily;

(g) dexamethasone (Decadron, Merck & Co.), dosage range from 0.25 mg daily to 18 mg daily;

(h) leflunomide, dosage range from 50 µg daily to 50 mg daily;

(i) cyclosporin A, dosage range from 0.1 mg daily to 100 mg daily;

(j) methylprednisolone (Medrol, Upjohn), dosage range from 1 mg daily to 250 mg daily, or alternate day dosing;

(k) eicosapentaenoic acid (or commercial products containing this substance as the active ingredient, including MaxEPA capsules, 18 gm of which contains 3.2 gm eicosapentaenoic acid), dosage range from 500 mg daily to 10 gm daily.

(l) hydrocortisone (Hydrocortone, Merck & Co.), dosage range from 1 mg daily to 400 mg daily;

(m) prednisolone (Pediapred, Fisons), dosage range from 1 mg daily or every other day to 250 mg daily;

(n) cortisone (Cortone, Merck & Co.), dosage range from 5 mg

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daily to 400 mg daily;

(o) prednisone (*Deltasone*, Upjohn), dosage range from 1 mg daily to 250 mg daily, or alternate day dosing;

(p) methylprednisolone acetate (*Depo-Medrol*, Upjohn), intra-synovial, intralesional or intramuscular dosage range from 0.5 mg daily to 50 mg daily, or weekly dosage of from 20 mg to 120 mg;

(q) triamcinolone (*Aristocort*, Fujisawa), dosage range from 1 mg daily to 200 mg daily, or alternate day dosing;

(r) triamcinolone diacetate (*Aristocort* suspensions, Fujisawa), intramuscular, intrasynovial or intralesional dosage range from 1 mg daily to 200 mg daily, or alternate day dosing;

(s) dexamethasone (*Decadron* phosphate injection, Merck & Co.), intramuscular, intravenous or intralesional dosage range from 0.1 mg daily to 10 mg daily;

(t) cortisone (*Cortone* suspension, Merck & Co.), intramuscular dosage range from 5 mg daily to 400 mg daily;

(u) hydrocortisone (*Hydrocortone* phosphate injection, Merck & Co.), intramuscular, intravenous or subcutaneous dosage range from 1 mg daily to 400 mg daily;

(v) hydrocortisone (*Hydrocortone* acetate suspension, Merck & Co.), intra-articular, intralesional or soft tissue injection dosage range from 1 mg daily to 400 mg daily;

(w) prednisolone (*Hydeltrasol* injection, Merck & Co.), intravenous, intramuscular, intra-articular, intralesional and soft tissue dosage range from 1 mg daily to 100 mg daily;

(x) triamcinolone acetonide (*Aristocort A* topical cream, Fujisawa), dosage range of from one to four applications per day to affected skin areas;

(y) fluocinolone acetonide (*Synalar-HP* cream, Syntex), dosage range of from one to four applications per day to affected skin areas;

(z) fluocinonide (*Lidex* gel, Syntex), dosage range of from one to four applications per day to affected skin areas;

(a') flurandrenolide 0.05% cream, lotion or ointment, dosage range of from one to four applications per day to affected skin areas;

(b') betamethasone valerate (*Betatrex* ointment, Savage Labor-

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 atories), dosage range of from one to four applications per day to affected skin areas;

(c') betamethasone 17,21-dipropionate (*Diprolene*, Schering), dosage range of from one to three applications per day;

(d') aspirin, dosage range from 300 mg daily to 6.5 gm daily;

(e') azathioprine (*Imuran*, Burroughs Wellcome), dosage range from 0.1 mg/kg daily to 2.5 mg/kg daily; and

(f') cyclophosphamide, dosage range from 0.1 mg/kg daily to 5 mg/kg daily.

The following illustrate specific formulations according to the present invention.

3,5-diaminobenzoic acid	1 gm
(+)- α -tocopherol acetate	500 I.U.
hydroxychloroquine	50 mg
 p-aminophenylacetic acid	 20 gm
mixed tocopherols	3,500 I.U.
15-deoxyspergualin	500 mg
 4-guanidinobenzoic acid, potassium salt	 5 gm
coenzyme Q	200 mg
cyclophosphamide	150 mg

Example 13

Clinical treatment of pneumoconiosis due to inhalation of asbestos particles (asbestosis), inhalation of stone dust or quartz (silic-osis) or inhalation of other causitive agents such as graphite, coal dust, particles produced by metal grinding, talc or corn dust can be improved by use of a composition comprising from about 1 gm to about 20 gm of at least one primary therapeutic agent comprising a primary amine benzoic acid derivative having a molecular weight of from about 100 to about 1,400 Daltons, and optionally at least one substance selected from those noted above in section (v) through section (ix), and a medicament recognized as effective to treat pneumoconiosis due to inhalation of asbestos particles (asbestosis), inhalation of stone dust or quartz (silico-sis) or inhalation of other causitive agents such as graphite,

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coal dust, particles produced by metal grinding, talc or corn dust, such as, for example,

- (a) D-penicillamine (Cuprimine, Merck & Co.), dosage range from 25 mg daily to 1.5 gm daily;
- (b) 4H-4-phenylthieno-[3,2-c]-[1]-benzopyran-2-carboxylic acid, dosage range from 0.5 mg/kg daily to 50 mg/kg daily;
- (c) 4H-2-carboxamido-4-phenylthieno-[3,2-c]-[1]-benzopyran, dosage range from 0.5 mg/kg daily to 50 mg/kg daily;
- (d) N-acetylcysteine, dosage range from 10 mg/kg daily to 150 mg/kg daily;
- (e) dexamethasone (Decadron, Merck & Co.), dosage range from 0.25 mg daily to 18 mg daily;
- (f) indomethacin (Indocin), dosage range from 25 mg daily to 250 mg daily;
- (g) prednisolone (Pediapred, Fisons), dosage range from 1 mg daily or every other day to 250 mg daily;
- (h) hydrocortisone (Hydrocortone, Merck & Co.), dosage range from 1 mg daily to 400 mg daily;
- (i) hydrocortisone (Hydrocortone phosphate injection, Merck & Co.), intramuscular, intravenous or subcutaneous dosage range from 1 mg daily to 400 mg daily;
- (j) flurbiprofen (Ansaid), dosage range from 50 mg daily to 500 mg daily;
- (k) S-carboxymethylcysteine, dosage range from 1 mg/kg daily to 100 mg/kg daily; and
- (l) dexamethasone (Decadron phosphate injection, Merck & Co.), intramuscular, intravenous or intralesional dosage range from 0.1 mg daily to 10 mg daily.

The following illustrate specific formulations according to the present invention.

3,5-diaminophenylacetic acid	1 gm
butylated hydroxyanisole	10 mg
N-acetylcysteine	500 mg
p-aminobenzoic acid	20 gm
2-aminomethyl-4-tert-butyl-6-propionylphenol	20 gm
prednisolone	100 mg

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4-amino-2-methoxycyclohexanecarboxylic acid	5 gm
tert-butylhydroquinone	500 mg
D-penicillamine	100 mg

Example 14

Clinical treatment of chronic obstructive pulmonary disease can be improved by use of a composition comprising from about 1 gm to about 20 gm of at least one primary therapeutic agent comprising a primary amine benzoic acid derivative having a molecular weight of from about 100 to about 1,400 Daltons, and optionally at least one substance selected from those noted above in section (v) through section (ix), and a medicament recognized as effective to treat chronic obstructive pulmonary disease, such as, for example,

(a) D-penicillamine (Cuprimine, Merck & Co.), dosage range from 25 mg daily to 1.5 gm daily;

(b) 4H-4-phenylthieno-[3,2-c]-[1]-benzopyran-2-carboxylic acid, dosage range from 0.5 mg/kg daily to 50 mg/kg daily;

(c) 4H-2-carboxamido-4-phenylthieno-[3,2-c]-[1]-benzopyran, dosage range from 0.5 mg/kg daily to 50 mg/kg daily;

(d) N-acetylcysteine, dosage range from 10 mg/kg daily to 150 mg/kg daily;

(e) dexamethasone (Decadron, Merck & Co.), dosage range from 0.25 mg daily to 18 mg daily;

(f) indomethacin (Indocin), dosage range from 25 mg daily to 250 mg daily;

(g) prednisolone (Pediapred, Fisons), dosage range from 1 mg daily or every other day to 250 mg daily;

(h) hydrocortisone (Hydrocortone, Merck & Co.), dosage range from 1 mg daily to 400 mg daily;

(i) hydrocortisone (Hydrocortone phosphate injection, Merck & Co.), intramuscular, intravenous or subcutaneous dosage range from 1 mg daily to 400 mg daily;

(j) flurbiprofen (Ansaid), dosage range from 50 mg daily to 500 mg daily;

(k) S-carboxymethylcysteine, dosage range from 1 mg/kg daily to 100 mg/kg daily;

(l) dexamethasone (Decadron phosphate injection, Merck & Co.), intramuscular, intravenous or intralesional dosage range

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from 0.1 mg daily to 10 mg daily;

(m) prednisone (*Deltasone*, Upjohn), dosage range from 1 mg daily to 250 mg daily, or alternate day dosing;

(n) methylprednisolone (*Medrol*, Upjohn), dosage range from 1 mg daily to 250 mg daily, or alternate day dosing; and

(o) methylprednisolone (*Solu Medrol*, Upjohn), intravenous or intramuscular dosage range from 0.25 mg/kg daily to 3 mg/kg daily.

The following illustrate specific formulations according to the present invention.

4-amino-2-methylphenylacetic acid	1 gm
N-acetylcysteine	500 mg
4H-2-carboxamido-4-phenylthieno-[3,2-c]-[1]-benzopyran	25 mg

p-aminobenzoic acid, potassium salt	20 gm
2-aminomethyl-4-tert-butyl-6-iodophenol	20 gm
flurbiprofen	500 mg

4-amino-2-methoxybenzoic acid, potassium salt	5 gm
acetyl-L-carnitine	1.5 gm
methylprednisolone	50 mg

Example 15

Clinical treatment of inflammatory myopathies can be improved by use of a composition comprising from about 1 gm to about 20 gm of at least one primary therapeutic agent comprising a primary amine benzoic acid derivative having a molecular weight of from about 100 to about 1,400 Daltons, and optionally at least one substance selected from those noted above in section (v) through section (ix), and a medicament recognized as effective to treat inflammatory myopathies disease, such as, for example,

(a) prednisone (*Deltasone*, Upjohn), dosage range from 1 mg daily to 250 mg daily, or alternate day dosing;

(b) methotrexate (*Rheumatrex*, Lederle Laboratories), dosage range from 1 mg weekly to 20 mg weekly;

(c) methotrexate sodium (*Methotrexate LPF*, Lederle), intramuscular, intravenous, intra-arterial or intrathecal dosage

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range from 2.5 mg daily to 30 mg daily, or doses from 5 mg to 50 mg once or twice weekly;

(d) cyclophosphamide (Cytoxan, Bristol-Myers Oncology), dosage range from 0.1 mg/kg daily to 5 mg/kg daily;

(e) cyclophosphamide (Cytoxan for injection, Bristol-Myers Oncology), dosage range from 0.1 mg/kg daily to 5 mg/kg daily, 2 mg/kg to 5 mg/kg twice weekly or 10 mg/kg to 15 mg/kg every seven to ten days;

(f) chlorambucil (Leukeran, Burroughs Wellcome), dosage range from 0.5 mg daily to 10 mg daily; and

(g) azathioprine (Imuran, Burroughs Wellcome), dosage range from 0.1 mg/kg daily to 2.5 mg/kg daily;

(h) diazepam (Valium, Roche Products), dosage range from 2 mg daily to 40 mg daily;

(i) diazepam (Valium injectable, Roche Products), dosage range from 2 mg daily to 40 mg daily; and

(j) diazepam (Valrelease, Roche Laboratories), dosage range from 5 mg daily to 30 mg daily.

The following illustrate specific formulations according to the present invention.

4-(aminoguanidino)benzoic acid	1 gm
ebselen	250 mg
prednisone	1 mg
p-guanidinobenzoic acid, potassium salt	20 gm
5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]- methylene]-3-(dimethylamino)-4-thiazolidinone	7.5 gm
cyclophosphamide	500 mg
4-amino-2-methoxybenzoic acid, potassium salt	5 gm
acetylhomocysteine thiolactone	750 mg
chlorambucil	5 mg

Example 16

Clinical treatment of inflammatory neuropathies can be improved by use of a composition comprising from about 1 gm to about 20 gm of at least one primary therapeutic agent comprising a primary amine benzoic acid derivative having a molecular

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weight of from about 100 to about 1,400 Daltons, and optionally at least one substance selected from those noted above in section (v) through section (ix), and a medicament recognized as effective to treat inflammatory neuropathies disease, such as, for example,

- (a) cortisone (Cortone, Merck & Co.), dosage range from 5 mg daily to 400 mg daily;
- (b) prednisone (Deltasone, Upjohn), dosage range from 1 mg daily to 250 mg daily, or alternate day dosing;
- (c) methylprednisolone (Medrol, Upjohn), dosage range from 1 mg daily to 250 mg daily, or alternate day dosing;
- (d) methylprednisolone acetate (Depo-Medrol, Upjohn), intra-synovial, intralesional or intramuscular dosage range from 0.5 mg daily to 50 mg daily, or weekly dosage of from 20 mg to 120 mg;
- (e) triamcinolone (Aristocort, Fujisawa), dosage range from 1 mg daily to 200 mg daily, or alternate day dosing;
- (f) triamcinolone diacetate (Aristocort suspensions, Fujisawa), intramuscular, intrasynovial or intralesional dosage range from 1 mg daily to 200 mg daily, or alternate day dosing;
- (g) betamethasone (Celestone, Schering), dosage range from 0.2 mg daily to 12 mg daily, or alternate day dosing;
- (h) betamethasone (Celestone Soluspan suspension, Schering), intramuscular or intralesional dosage range from 0.1 mg daily to 10 mg daily, or alternate day dosing;
- (i) dexamethasone (Decadron, Merck & Co.), dosage range from 0.25 mg daily to 18 mg daily;
- (j) dexamethasone (Decadron phosphate injection, Merck & Co.), intramuscular, intravenous or intralesional dosage range from 0.1 mg daily to 10 mg daily;
- (k) cortisone (Cortone suspension, Merck & Co.), intramuscular dosage range from 5 mg daily to 400 mg daily;
- (l) hydrocortisone (Hydrocortone, Merck & Co.), dosage range from 1 mg daily to 400 mg daily;
- (m) hydrocortisone (Hydrocortone phosphate injection, Merck & Co.), intramuscular, intravenous or subcutaneous dosage range from 1 mg daily to 400 mg daily;
- (n) prednisolone (Hydeltrasol injection, Merck & Co.), intra-

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venous, intramuscular, intra-articular, intralesional and soft tissue dosage range from 1 mg daily to 100 mg daily;

(o) prednisolone (Pediapred, Fisons), dosage range from 1 mg daily or every other day to 250 mg daily; and

(p) ebselen, intravenous, intramuscular, subcutaneous or oral dosage range from 5 mg/kg daily to 500 mg/kg daily.

The following illustrate specific formulations according to the present invention.

4-aminocyclohexanecarboxylic acid	1 gm
d- α -tocopheryl acetate	500 I.U.
prednisone	1 mg
p-aminophenylacetic acid, potassium salt	20 gm
2,6-di-tert-butyl-4-[2'-thenoyl]phenol	20 gm
betamethasone	12 mg
4-amino-2-hydroxybenzoic acid	5 gm
L-methionine	2 gm
hydrocortisone	50 mg

Example 17

Clinical treatment of epilepsy can be improved by use of a composition comprising from about 1 gm to about 20 gm of at least one primary therapeutic agent comprising a primary amine benzoic acid derivative having a molecular weight of from about 100 to about 1,400 Daltons, and optionally at least one substance selected from those noted above in section (v) through section (ix), and a medicament recognized as effective to treat epilepsy, such as, for example,

- (a) dizocilpine (Neurogard, Merck Sharp & Dohme), dosage range from 0.1 μ g/kg daily to 10 mg/kg daily;
- (b) phenytoin (Dilantin-125, Parke-Davis), dosage range from 50 mg daily to 625 mg daily;
- (c) phenytoin-polyvinylpyrrolidone coprecipitate, dosage range from 50 mg daily to 1 gm daily;
- (d) phenytoin in combination with phenobarbital (Dilantin capsules, Parke-Davis), dosage range from 100 mg phenytoin sodium and 16 mg phenobarbital daily to 600 mg phenytoin

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- sodium and 192 mg phenobarbital daily;
- (e) phenobarbital (Lilly), dosage range from 5 mg daily to 200 mg daily;
 - (f) primidone (Mysoline, Wyeth-Ayerst Laboratories), dosage range from 25 mg daily to 1.75 gm daily;
 - (g) carbamazepine (Tegretol, Basel), dosage range from 50 mg daily to 1.2 gm daily;
 - (h) ethosuximide (Zarontin, Parke-Davis), dosage range from 250 mg daily to 2 gm daily;
 - (i) clonazepam (Klonopin, Roche Laboratories), dosage range from 0.5 mg daily to 20 mg daily;
 - (j) valproic acid (Depakene, Abbott Laboratories), dosage range from 1 mg/kg daily to 60 mg/kg daily;
 - (k) divalproex sodium (Depakote, Abbott Laboratories), dosage range from 1 mg/kg daily to 60 mg/kg daily;
 - (l) acetazolamide (Diamox, Lederle), dosage range from 50 mg daily to 2 gm daily;
 - (m) acetazolamide sodium (Diamox, Lederle), intravenous dosage range from 50 mg daily to 2 gm daily;
 - (n) prednisone (Deltasone, Upjohn), dosage range from 1 mg daily to 250 mg daily, or alternate day dosing;
 - (o) corticotropin, intramuscular dosage range from 5 units daily to 60 units daily;
 - (p) diazepam (Valium, Roche Products), dosage range from 2 mg daily to 40 mg daily;
 - (q) diazepam (Valium injectable, Roche Products), dosage range from 2 mg daily to 40 mg daily;
 - (r) lorazepam (Ativan, Wyeth-Ayerst Laboratories), intravenous dosage range from 50 µg/kg daily to 300 µg/kg daily;
 - (s) felbamate (Felbatol, Wallace Laboratories), intravenous, intramuscular, subcutaneous or oral dosage range from 100 µg/kg daily to 2 mg/kg daily;
 - (t) zonisamide (Excegran, Dainippon), intravenous, intramuscular, subcutaneous or oral dosage range from 100 µg/kg daily to 2 mg/kg daily;
 - (u) gabapentin (Neurontin, Warner-Lambert), dosage range from 100 µg/kg daily to 2 mg/kg daily;
 - (v) lamotrigine (Lamictal, Burroughs Wellcome), dosage range

from 100 $\mu\text{g/kg}$ daily to 2 mg/kg daily; and
 (w) vigabatrin (Sabril, Marion Merrell Dow), dosage range from 100 $\mu\text{g/kg}$ daily to 2 mg/kg daily.
 The following illustrate specific formulations according to the present invention.

5-amino-2-hydroxybenzoic acid	1 gm
d- α -tocopheryl succinate	750 I.U.
phenytoin	50 mg
p-aminobenzoic acid	10 gm
ebselen	10 gm
dizocilpine	500 mg
4-aminophenylacetic acid	5 gm
prostaglandin B ₁ oligomers	7.5 gm
primidone	1 gm

Example 18

Clinical treatment of Alzheimer's disease can be improved by use of a composition comprising from about 1 gm to about 20 gm of at least one primary therapeutic agent comprising a primary amine benzoic acid derivative having a molecular weight of from about 100 to about 1,400 Daltons, and optionally at least one substance selected from those noted above in section (v) through section (ix), and a medicament recognized as effective to treat Alzheimer's disease, such as, for example,

(a) vasodilator or other nootropic direct brain metabolic enhancer drugs such as

idebenone, dosage range from 5 mg/kg daily to 150 mg/kg daily;
 propentophylline, intravenous, intramuscular, subcutaneous or oral dosage range from 50 mg daily to 3 gm daily;

pentoxifylline, dosage range from 50 mg daily to 3 gm daily;
 citicoline, dosage range from 50 mg daily to 5 gm daily;

ebiratide, subcutaneous dosage range from 3 $\mu\text{g/kg}$ daily to 1 mg/kg daily;

vinpocetine (Cavinton, Chemical Works of Gedeon Richter, Ltd.), intravenous, intramuscular, subcutaneous or oral dosage

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range from 5 mg/kg daily to 300 mg/kg daily;
bromvincamine, dosage range from 25 mg daily to 3 gm daily;
cyclandelate, dosage range from 25 mg daily to 3 gm daily;
isoxsuprene, dosage range from 25 mg daily to 3 gm daily;
nafronyl, dosage range from 25 mg daily to 3 gm daily;
papaverine, dosage range from 25 mg daily to 3 gm daily;
suloctidil, dosage range from 25 mg daily to 3 gm daily;
vinburnine, dosage range from 25 mg daily to 3 gm daily;
vincamine, dosage range from 25 mg daily to 3 gm daily;
vindeburnol, dosage range from 25 mg daily to 3 gm daily;
naloxone, intravenous, intramuscular, subcutaneous or oral
dosage range from 5 mg daily to 300 mg daily;
ethyl 5-isopropoxy-4-methyl- β -carboline-3-carboxylate,
intravenous, intramuscular, subcutaneous or oral dosage range
from 2 mg/kg daily to 100 mg/kg daily;
N'-methyl- β -carboline-3-carboxamide, intravenous, intramus-
cular, subcutaneous or oral dosage range from 2 mg/kg daily to
100 mg/kg daily;
methyl 6,7-dimethoxy-4-ethyl- β -carboline-3-carboxylate, intra-
venous, intramuscular, subcutaneous or oral dosage range from
0.1 mg/kg daily to 10 mg/kg daily;
ethyl 5-methoxy-4-ethyl- β -carboline-3-carboxylate, intraven-
ous, intramuscular, subcutaneous or oral dosage range from 1
mg/kg daily to 30 mg/kg daily;
ifenprodil tartrate, dosage range from 0.5 mg/kg daily to 120
mg/kg daily;
piracetam, dosage range from 1 mg daily to 100 mg daily;
aniracetam, dosage range from 50 mg/kg daily to 1 gm/kg daily;
pyroglutamic acid, intravenous, intramuscular, subcutaneous or
oral dosage range from 100 mg/kg daily to 5 gm/kg daily;
tenilsetam, dosage range from 10 mg daily (or alternate day)
to 1 gm daily (or alternate day), or from 25 mg once a week to
1 gm once a week;
pramiracetam, dosage range from 50 mg/kg daily to 8 gm/kg
daily;
oxiracetam, dosage range from 200 mg daily to 2 gm daily;
rolziracetam, intravenous, intramuscular, subcutaneous or oral
dosage range from 1 mg daily to 1 gm daily;
razobazam, intravenous, intramuscular, subcutaneous or oral

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dosage range from 0.1 mg/kg daily to 25 mg/kg daily;
exifone, intravenous, intramuscular, subcutaneous or oral
dosage range from 1 mg daily to 1 gm daily;
rolipram, intravenous, intramuscular, subcutaneous or oral
dosage range from 1 mg daily to 1 gm daily;
sabeluzole, dosage range from 2 mg daily to 40 mg daily;
nimodipine (Nimotop, Miles Pharmaceutical), dosage range from
300 mg daily to 3.6 gm daily;
flunarizine, dosage range from 2 mg daily to 100 mg daily;
nicergoline (Sermion), intravenous, intramuscular, subcuta-
neous or oral dosage range from 6 mg daily to 10 gm daily;
phosphatidylserine, intravenous or oral dosage range from 1
mg/kg daily to 250 mg/kg daily;
etiracetam, dosage range from 50 mg/kg daily to 8 gm/kg daily;
dupracetam, intravenous, intramuscular, subcutaneous or oral
dosage range from 1 mg daily to 1 gm daily; and
ergoloid mesylates (Hydergine, Sandoz Pharmaceuticals), dosage
range from 0.5 mg daily to 40 mg daily;

(b) neurotransmission enhancer drugs such as
amantadine (Symmetrel, Du Pont Multi-Source Products), dosage
range from 10 mg daily to 400 mg daily;
calcium hopantenate, dosage range from 100 mg daily to 4 gm
daily;

lisuride, dosage range from 0.1 mg daily to 2 mg daily; and
indeloxazine, dosage range from 50 mg daily to 1.5 gm daily;

(c) tiapride, dosage range from 1 mg daily to 400 mg daily;

(d) psychotherapeutic drugs such as

haloperidol (Haldol, McNeil Pharmaceutical), dosage range from
0.2 mg daily to 15 mg daily;

bromperidol, dosage range from 20 µg/kg daily to 0.25 mg/kg
daily;

thioridazine (Mellaril, Sandoz Pharmaceutical), dosage range
from 10 mg daily to 800 mg daily;

thiothixene (Navane, Roerig), dosage range from 2 mg daily to
60 mg daily;

fluphenazine (Prolixin, Apothecon), dosage range from 0.2 mg
daily to 40 mg daily;

perphenazine in amitriptyline/perphenazine combinations
(Etrafon, Schering), dosage range from 4 mg perphenazine and

50 mg amitriptyline daily to 16 mg perphenazine and 100 mg amitriptyline daily; and

molindone (Moban, Du Pont Multi-Source Products), dosage range from 3 mg daily to 225 mg daily;

(e) acetylcholinesterase inhibitors such as physostigmine (*Antilirium Injectable*, Forest Pharmaceuticals), oral dosage range from 0.1 mg daily to 20 mg daily, or intravenous, intramuscular or subcutaneous dosage range from 5 µg daily to 3 mg daily, optionally with phosphatidylcholine co-agent, oral dosage range from zero to 15 gm daily; heptylphysostigmine, dosage range from 1 mg daily to 1 gm daily;

tacrine (*Cognex*, Warner-Lambert), dosage range from 5 mg daily to 200 mg daily, optionally with phosphatidylcholine co-agent, dosage range from zero to 15 gm daily;

(*)-9-amino-1,2,3,4-tetrahydroacridin-1-ol, dosage range from 2 mg daily to 200 mg daily;

metrifonate, intramuscular, intravenous, subcutaneous or oral dosage range from 0.1 mg/kg daily to 125 mg/kg daily;

velnacrine (*Mentane*, Hoechst-Roussel), dosage range from 10 mg daily to 350 mg daily;

phenylmethylsulfonyl fluoride, intravenous, subcutaneous, intramuscular or oral dosage range from 5 mg/kg daily to 60 mg/kg daily;

methanesulfonyl fluoride, intravenous, intramuscular, subcutaneous or oral dosage range from 5 mg/kg daily to 350 mg/kg daily;

huperzine A, intramuscular, intravenous, subcutaneous or oral dosage range from 10 µg/kg daily to 1 mg/kg daily;

huperzine B, intramuscular, intravenous, subcutaneous or oral dosage range from 10 µg/kg daily to 1 mg/kg daily;

edrophonium chloride (*Hoffman LaRoche*), intravenous, intramuscular, subcutaneous or oral dosage range from 2 mg daily to 400 mg daily;

galanthamine, intravenous, intramuscular, subcutaneous or oral dosage range from 5 mg daily to 100 mg daily; and

miotine, intravenous, intramuscular, subcutaneous or oral dosage range from 2 mg daily to 400 mg daily;

(f) calcium channel blocker agents such as

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diltiazem (Cardizem or Cardizem SR), dosage range from 10 mg daily to 360 mg daily;
verapamil (Calan or Calan SR), dosage range from 10 mg daily to 480 mg daily;
nifedipine (Procardia), dosage range from 3 mg daily to 180 mg daily;
nifedipine (Procardia XL), dosage range from 3 mg daily to 90 mg daily;
nicardipine (Cardene), dosage range from 6 mg daily to 120 mg daily;
isradipine (DynaCirc), dosage range from 0.5 mg daily to 20 mg daily;
amlodipine (Norvasc, Pfizer Labs Division), dosage range from 0.5 mg daily to 10 mg daily; and
felodipine (Plendil, Merck & Co.), dosage range from 0.5 mg daily to 20 mg daily;

(g) biogenic amines and substances related thereto such as clonidine (Catapres, Boehringer Ingelheim), dosage range from 0.25 mg daily to 2.4 mg daily;

guanfacine (Tenex, Robins), dosage range from 0.25 mg daily to 3 mg daily;

alaproclate, dosage range from 0.25 mg daily to 3 mg daily;

fipexide, dosage range from 0.25 mg daily to 3 mg daily;

zimeldine, dosage range from 0.25 mg daily to 3 mg daily; and

citalopram, dosage range from 0.25 mg daily to 3 mg daily;

(h) antirage drugs such as

propranolol (Inderal, Wyeth-Ayerst Laboratories), dosage range from 30 mg daily to 640 mg daily;

carbamazepine (Tegretol, Geigy), dosage range from 40 mg daily to 1.6 gm daily; and

fluoxetine (Prozac Pulvules, Dista), dosage range from 20 mg daily to 80 mg daily;

(i) minor tranquilizers such as benzodiazepine agents including

diazepam (Valium, Roche Products), dosage range from 0.5 mg daily to 40 mg daily;

lorazepam (Ativan, Wyeth-Ayerst Laboratories), dosage range from 0.5 mg daily to 10 mg daily;

prazepam (Centrax, Parke-Davis), dosage range from 5 mg daily

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to 60 mg daily;

chlordiazepoxide (*Libritabs*, Roche Products), dosage range from 5 mg daily to 300 mg daily;

chlordiazepoxide/clidinium combination (*Librax*, Roche Products), dosage range from 5 mg chlordiazepoxide and 2.5 mg clidinium daily to 20 mg chlordiazepoxide and 10 mg clidinium daily;

chlordiazepoxide/amitriptyline combination (*Limbitrol DS*, Roche Products), dosage range from 10 mg chlordiazepoxide and 25 mg daily to 60 mg chlordiazepoxide and 150 mg amitriptyline daily;

chlordiazepoxide/esterified estrogen combination (*Menrium*, Roche Products), dosage range from 5 mg chlordiazepoxide and 0.2 mg esterified estrogen daily to 30 mg chlordiazepoxide and 1.2 mg esterified estrogen daily;

oxazepam (*Serax*, Wyeth-Ayerst), dosage range from 10 mg daily to 120 mg daily; and

clorazepate dipotassium (*Tranxene*, Abbott Laboratories), dosage range from 3.75 mg daily to 60 mg daily;

(j) angiotensin converting enzyme inhibitors such as captopril (*Capoten*, Squibb), dosage range from 5 mg daily to 300 mg daily;

captopril in combination with hydrochlorothiazide (*Capozide*, Squibb), dosage range from 5 mg captopril and 3 mg hydrochloro-thiazide daily to 150 mg captopril and 50 mg hydrochlorothiazide daily;

enalapril maleate (*Vasotec*, Merck & Co.), dosage range from 0.5 mg daily to 100 mg daily;

enalaprilat, dosage range from 0.5 mg daily to 100 mg daily;

enalapril maleate/hydrochlorothiazide combination (*Vaseretic*, Merck & Co.), dosage range from 2.5 mg enalapril maleate and 6.25 mg hydrochlorothiazide daily to 20 mg enalapril maleate and 50 mg hydrochlorothiazide daily;

fosinopril (*Monopril*, Mead Johnson Pharmaceuticals), dosage range from 2 mg daily to 60 mg daily;

lisinopril (*Zestril*, Stuart), dosage range from 1 mg daily to 40 mg daily;

ramipril (*Altace*, Hoechst-Roussel), dosage range from 0.5 mg daily to 10 mg daily;

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epi-captopril, dosage range from 1 mg daily to 300 mg daily;
alacepril, dosage range from 5 mg daily to 300 mg daily;
quinapril, dosage range from 0.5 mg daily to 40 mg daily;
perindopril, dosage range from 0.2 mg daily to 40 mg daily;
delapril, dosage range from 4 mg daily to 1.5 gm daily;
cilazapril, dosage range from 0.2 mg daily to 40 mg daily;
pivalopril, dosage range from 2 mg daily to 250 mg daily;
rentiapril, dosage range from 1 mg daily to 150 mg daily;
zofenopril, dosage range from 1 mg daily to 150 mg daily; and
zofenoprilat, dosage range from 1 mg daily to 150 mg daily;

(k) substances which may enhance acetylcholine synthesis,
storage or release such as

phosphatidylcholine, dosage range from 1 gm daily to 15 gm
daily;

4-aminopyridine, intravenous, intramuscular, subcutaneous or
oral dosage range from 0.25 mg/kg daily to 10 mg/kg daily;

3,4-diaminopyridine, intravenous, intramuscular, subcutaneous
or oral dosage range from 50 µg daily to 100 mg daily;

choline chloride, dosage range from 500 mg daily to 30 gm
daily; choline bitartrate, dosage range from 500 mg daily to
30 gm daily;

bifemelane, dosage range from 1 mg/kg daily to 1.2 gm/kg
daily;

vesamicol, dosage range from 50 µg/kg daily to 500 mg/kg
daily;

secoverine, dosage range from 50 µg/kg daily to 500 mg/kg
daily;

tetraphenylurea, dosage range from 50 µg/kg daily to 500 mg/kg
daily; and

nicotinamide, dosage range from 1 mg/kg daily to 500 mg/kg
daily;

(l) postsynaptic receptor agonists such as

arecoline, intravenous, intramuscular, subcutaneous or oral
dosage range from 2 mg daily to 25 mg daily;

oxotremorine, intravenous, intramuscular, subcutaneous or oral
dosage range from 1 µg/kg daily to 0.2 mg/kg daily;

ethyl nipecotate, intravenous, intramuscular, subcutaneous or
oral dosage range from 2 mg daily to 250 mg daily;

bethanechol (Urecholine, Merck & Co.), dosage range from 5 mg

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daily to 200 mg daily; and

levacecarnine (acetyl-L-carnitine or Alcar, Sigma-Tau), dosage range from 500 mg daily to 5 gm daily;

(m) ganglioside GM₁, intravenous, intramuscular or subcutaneous dosage range from 20 mg daily to 200 mg daily;

(n) mixed cow brain gangliosides (Cronassial, Fidia Pharmaceutical, marketed in several countries in Western Europe, South America and the Far East), intravenous, intramuscular or subcutaneous dosage range from 20 mg daily to 200 mg per day;

(o) specific monoamine oxidase-A inhibitors such as moclobemide (Aurorix, Hoffmann-La Roche), dosage range from 50 mg daily to 600 mg daily;

(p) N-methyl-D-aspartate glutamate receptor antagonists administered orally, intravenously, intramuscularly or subcutaneously such as

milacemide, dosage range from 50 mg daily to 2.5 gm daily;

trihexyphenidyl (Artane, Lederle), dosage range from 0.1 mg daily to 20 mg daily;

ethopropazine (Paridol), dosage range from 10 mg daily to 400 mg daily;

procyclidine (Kemadrin, Burroughs Wellcome), dosage range from 1 mg daily to 40 mg daily;

diphenhydramine (Benadryl, Parke-Davis), dosage range from 5 mg daily to 200 mg daily;

dizocilpine (Neurogard, Merck Sharp & Dohme), dosage range from 0.1 µg/kg daily to 10 mg/kg daily;

amantadine (Symmetrel, Du Pont Multi-Source Products), dosage range from 10 mg daily to 400 mg daily; and

memantine, dosage range from 10 mg daily to 400 mg daily;

(q) nonsteroidal anti-inflammatory agents such as those recognized for treatment of rheumatoid arthritis, including

flurbiprofen (Ansaid, Upjohn), dosage range from 20 mg daily to 300 mg daily;

aspirin (Arthritis Pain Formula, Whitehall Laboratories), dosage range from 250 mg aspirin daily to 4 gm daily;

mesalamine (Asacol, Procter & Gamble Pharmaceuticals), dosage range from 250 mg daily to 2.4 gm daily;

phenylbutazone (Butazolidin, Geigy), dosage range from 30 mg daily to 400 mg daily;

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sulindac (Clinoril, Merck & Co), dosage range from 40 mg daily to 400 mg daily;

D-penicillamine (Cuprimine, Merck & Co.), dosage range from 25 mg daily to 2 gm daily;

oxaprozin (Daypro, Searle), dosage range from 25 mg daily to 2 gm daily;

salsalate (Disalcid, 3M Pharmaceuticals), dosage range from 300 mg daily to 3 gm daily;

diflunisal (Dolobid, Merck & Co.), dosage range from 100 mg daily to 1.5 gm daily;

piroxicam (Feldene, Pfizer Labs Division), dosage range from 2 mg daily to 20 mg daily;

indomethacin (Indocin, Merck & Co.), dosage range from 10 mg daily to 200 mg daily;

etodolac (Lodine, Wyeth-Ayerst Laboratories), dosage range from 100 mg daily to 1.2 gm daily;

meclofenamate sodium (Meclofen, Parke-Davis), dosage range from 20 mg daily to 400 mg daily;

ibuprofen (Motrin, Upjohn), dosage range from 100 mg daily to 3.2 gm daily;

fenoprofen calcium (Nalfon, Dista), dosage range from 100 mg daily to 3.2 gm;

naproxen sodium (Anaprox, Syntex), dosage range from 50 mg daily to 1.65 gm daily;

naproxen (Naprosyn, Syntex), dosage range from 50 mg daily to 1.5 gm daily;

ketoprofen (Orudis, Wyeth-Ayerst), dosage range from 15 mg daily to 300 mg daily;

mefenamic acid (Ponstel, Parke-Davis), dosage range from 150 mg daily to 1.5 gm daily;

nabumetone (Relafen, SmithKline Beecham), dosage range from 100 mg daily to 2 gm daily;

auranofin (Ridaura, SmithKline Beecham), dosage range from 1 mg daily to 9 mg daily;

tolmetin sodium (Tolectin, McNeil Pharmaceutical), dosage range from 100 mg daily to 1.8 gm daily;

ketorolac tromethamine (Toradol, Syntex Laboratories), dosage range from 4 mg daily to 40 mg daily;

diclofenac sodium (Voltaren, Geigy), dosage range from 10 mg

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daily to 200 mg daily; and

deferoxamine mesylate (*Desferal*, CIBA Pharmaceutical), intravenous, intramuscular or subcutaneous dosage range from 100 mg daily to 2 gm daily;

(r) selegiline (*Eldepryl*, Somerset), dosage range from 5 mg daily to 10 mg daily;

(s) thiamine, dosage range from 500 mg daily to 3 gm daily;

(t) anfacine, intravenous, intramuscular, subcutaneous or oral dosage range from 1 mg/kg daily to 350 mg/kg daily;

(u) sulbutiamine (*Arcalion*, Laboratories Servier), dosage range from 1 mg/kg daily to 350 mg/kg daily;

(v) anti-oxidant agents which may be used in combination such as

ascorbic acid, dosage range from 1 mg daily to 60 mg daily;

α -tocopherol, dosage range from 100 I. U. daily to 3,500 I. U. daily;

N-acetylcysteine, dosage range from 100 mg daily to 1 gm daily;

β -carotene, dosage range from 20 mg daily to 300 mg daily;

penicillamine, dosage range from 25 mg daily to 2 gm daily;

cysteamine, dosage range from 200 mg daily to 4 gm daily;

deferoxamine mesylate (*Desferal*, CIBA Pharmaceutical), intravenous, intramuscular or subcutaneous dosage range from 100 mg daily to 2 gm daily; and

ebselen, dosage range from 5 mg/kg daily to 1 gm/kg daily;

(w) specific monoamine oxidase-B inhibitors such as lazabemide (Hoffmann-La Roche), dosage range from 10 mg daily to 200 mg daily;

(x) linopirdine (*Aviva*, DuPont Merck), dosage range from 1 mg daily to 500 mg daily;

(y) D-cycloserine, dosage range from 0.1 mg/kg daily to 15 mg/kg daily;

(z) serotonergic receptor antagonists such as ketanserin (*Ketan*, Janssen Pharmaceutica), intravenous, intramuscular, subcutaneous or oral dosage range from 0.1 mg/kg daily to 20 mg/kg daily; and

mianserin (*Mian*, Organon International), intravenous, intramuscular, subcutaneous or oral dosage range from 0.1 mg/kg daily to 20 mg/kg daily; and

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(a') estrogen, dosage range from 0.2 mg daily to 1.2 mg daily. The following illustrate specific formulations according to the present invention.

trans-4-aminocyclohexane-	
carboxylic acid	1 gm
d- α -tocopherol	500 I.U.
N'-methyl- β -carboline-3-carboxamide	200 mg
p-aminobenzoic acid, potassium salt	15 gm
2-(2-hydroxy-4-methylphenyl)-	
aminothiazole hydrochloride	4 gm
lazabemide	200 mg
4-guanidinophenylacetic acid	5 gm
tert-butylhydroquinone	500 mg
dizocilpine	100 mg

Example 19

Clinical treatment of myasthenia gravis can be improved by use of a composition comprising from about 1 gm to about 20 gm of at least one primary therapeutic agent comprising a primary amine benzoic acid derivative having a molecular weight of from about 100 to about 1,400 Daltons, and optionally at least one substance selected from those noted above in section (v) through section (ix), and a medicament recognized as effective to treat myasthenia gravis, such as, for example,

(a) prednisone (Deltasone, Upjohn), dosage range from 1 mg daily to 250 mg daily, or alternate day dosing;

(b) azathioprine (Imuran, Burroughs Wellcome), dosage range from 0.1 mg/kg daily to 2.5 mg/kg daily;

(c) pyridostigmine (Mestinon, ICN), dosage range from 100 mg daily to 1.5 gm daily;

(d) pyridostigmine (Mestinon injectable, ICN), intramuscular or slow intravenous dosage range from 100 mg daily to 1.5 gm daily;

(d) neostigmine bromide (Prostigmin, ICN), dosage range from 5 mg daily to 375 mg daily;

(e) neostigmine methylsulfate (Prostigmin injectable, ICN),

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intramuscular or subcutaneous dosage range from 0.5 mg daily to 10 mg daily;

(f) atropine, dosage range from 0.2 mg daily to 2 mg daily;

(g) propantheline (Pro-Banthine, Schiapparelli Searle), dosage range from 15 mg daily to 75 mg daily; and

(h) ephedrine, dosage range from 10 mg daily to 100 mg daily.

The following illustrate specific formulations according to the present invention.

4-amino-2-methylbenzoic acid	1 gm
mixed tocopherols	500 I.U.
pyridostigmine	100 mg
4-amino-2-methoxybenzoic acid, potassium salt	15 gm
D-myo-inositol-1.2.6-trisphosphate	20 gm
azathioprine	150 mg
4-(aminoguanidino)phenylacetic acid	5 gm
deferoxamine mesylate	200 mg
propantheline	25 mg

Example 20

Clinical treatment of multiple sclerosis can be improved by use of a composition comprising from about 1 gm to about 20 gm of at least one primary therapeutic agent comprising a primary amine benzoic acid derivative having a molecular weight of from about 100 to about 1,400 Daltons, and optionally at least one sub-stance selected from those noted above in section (v) through section (ix), and a medicament recognized as effective to treat multiple sclerosis, such as, for example,

(a) 15-deoxyspergualin, intravenous, intramuscular, subcutaneous or oral dosage range from 0.5 mg/kg daily to 10 mg/kg daily;

(b) leflunomide, dosage range from 50 μ g daily to 50 mg daily;

(c) methylprednisolone (Medrol, Upjohn), dosage range from 1 mg daily to 250 mg daily, or alternate day dosing;

(d) prednisone (Deltasone, Upjohn), dosage range from 1 mg

- daily to 250 mg daily, or alternate day dosing;¹⁰⁰
- (e) dexamethasone (Decadron, Merck & Co.), dosage range from 0.1 mg daily or every other day to 10 mg daily or every other day;
- (f) corticotropin (Depo-ACTH, Upjohn), intravenous, intramuscular or subcutaneous dosage range from from 10 units daily to 150 units daily;
- (g) cyclosporin A (Sandimmune, Sandoz Pharmaceutical), dosage range from 1 mg/kg daily to 15 mg/kg daily;
- (h) amantadine (Symmetrel, Du Pont Multi-Source Products), dosage range from 10 mg daily to 400 mg daily;
- (i) diazepam (Valium, Roche Products), dosage range from 0.5 mg daily to 40 mg daily;
- (j) clonazepam (Klonopin, Roche Laboratories), dosage range from 0.5 mg daily to 20 mg daily;
- (k) carbamazepine (Tegretol, Geigy), dosage range from 40 mg daily to 1.6 gm daily;
- (l) phenytoin (Dilantin-125, Parke-Davis), dosage range from 50 mg daily to 625 mg daily;
- (m) isoniazid (INH isoniazid, CIBA), dosage range from 10 mg daily to 300 mg daily;
- (n) primidone (Mysoline, Wyeth-Ayerst Laboratories), dosage range from 25 mg daily to 1.75 gm daily;
- (o) propranolol (Inderal, Wyeth-Ayerst Laboratories), dosage range from 30 mg daily to 640 mg daily;
- (p) amitriptyline (Elavil, Stuart), dosage range from 50 mg daily to 300 mg daily;
- (q) oxybutynin (Ditropan, Marion Merrell Dow), dosage range from 2.5 mg daily to 20 mg daily;
- (r) propantheline (Pro-Banthine, Schiapparelli Searle), dosage range from 2.5 mg daily to 75 mg daily;
- (s) imipramine, dosage range from 2 mg daily to 150 mg daily;
- (t) carbachol, dosage range from 50 µg/kg daily to 5 mg/kg daily;
- (u) bethanechol (Urecholine, Merck & Co.), dosage range from 5 mg daily to 200 mg daily;
- (v) phenoxybenzamine (Dibenzylamine, SmithKline Beecham), dosage range from 5 mg daily to 150 mg daily;
- (w) tizanidine, dosage range from 50 µg/kg daily to 5 mg/kg

daily;

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(x) chlorpromazine (Thorazine, SmithKline Beecham), dosage range from 10 mg daily to 200 mg daily;

(y) baclofen (Atrofen, Athena Neurosciences), dosage range from 1 mg daily to 80 mg daily;

(z) diacetylrhein, dosage range from 10 mg daily to 500 mg daily;

(a') alfa-2a interferon (Roferon-A, Roche Laboratories), intravenous, intramuscular or subcutaneous dosage range from 300,000 IU daily to 36,000,000 IU daily;

(b') alfa-2b interferon (Intron-A, Schering), intravenous, intramuscular or subcutaneous dosage range from 300,000 IU daily to 5,000,000 IU daily;

(c') alfa-N3 interferon (Alferon N Injection, Purdue Frederick), intravenous, intramuscular or subcutaneous dosage range from 250,000 IU daily to 2,500,000 IU daily;

(d') beta interferon (Betaseron, Berlex), intravenous, intramuscular or subcutaneous dosage range from 5,000 U/kg daily to 50,000 U/kg daily;

(e') gamma-1b interferon (Actimmune, Genentech), intravenous, intramuscular or subcutaneous dosage range from 5,000 U/kg daily to 50,000 U/kg daily;

(f') copolymer-1 (random polymer of L-alanine, L-glutamic acid, L-lysine and L-tyrosine, ratio of 6.0:1.9:4.7:1.0, of molecular weight between 14,000 and 23,000 Daltons), intravenous, subcutaneous or intramuscular dosage range 2 mg daily to 40 mg daily;

(g') 4-aminopyridine, intravenous, intramuscular, subcutaneous or oral dosage range from 0.25 mg/kg daily to 10 mg/kg daily;

(h') 3,4-diaminopyridine, dosage range from 50 µg daily to 100 mg daily;

(i') cyclophosphamide (Cytosan, Bristol-Myers Oncology), dosage range from 0.1 mg/kg daily to 5 mg/kg daily;

(j') cyclophosphamide (Cytosan for injection, Bristol-Myers Oncology), intravenous, intramuscular or subcutaneous dosage range from 0.1 mg/kg daily to 5 mg/kg daily, 2 mg/kg to 5 mg/kg twice weekly or 10 mg/kg to 15 mg/kg every seven to ten days;

(k') prednisolone (Pediapred, Fisons), dosage range from 1 mg

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daily or every other day to 250 mg daily;

(l') methylprednisolone acetate (*Depo-Medrol*, Upjohn), intra-synovial, intralesional or intramuscular dosage range from 0.5 mg daily to 50 mg daily, or weekly dosage of from 20 mg to 120 mg;

(m') triamcinolone (*Aristocort*, Fujisawa), dosage range from 1 mg daily to 200 mg daily, or alternate day dosing;

(n') triamcinolone diacetate (*Aristocort* suspensions, Fujisawa), intramuscular, intrasynovial or intralesional dosage range from 1 mg daily to 200 mg daily, or alternate day dosing;

(o') methylprednisolone (*Solu Medrol*, Upjohn), intramuscular or intravenous maintenance dosage range from 0.25 mg/kg daily to 3 mg/kg daily;

(p') azathioprine (*Imuran*, Burroughs Wellcome), dosage range from 5 mg daily to 300 mg daily; and

(q') bovine myelin, dosage range from 25 mg daily to 1 gm daily.

The following illustrate specific formulations according to the present invention.

4-guanidino-2-methylbenzoic acid	1 gm
prostaglandin B ₁ oligomers	300 mg
diacetylrhein	10 mg
4-amino-2-hydroxybenzoic acid	20 gm
N,N'-dimethylthiourea	5 gm
baclofen	80 mg
4-(aminoguanidino)-2-methoxyphenylacetic acid	5 gm
N,N'-diphenyl-p-phenylenediamine	10 gm
carbamazepine	500 mg

Example 21

Clinical treatment of inflammatory site edema can be improved by use of a composition comprising from about 1 gm to about 20 gm of at least one primary therapeutic agent comprising a primary amine benzoic acid derivative having a molecular weight of from about 100 to about 1,400 Daltons, and option-

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ally at least one substance selected from those noted above in section (v) through section (ix), and a medicament recognized as effective to treat inflammatory site edema, such as, for example,

- (a) cyproheptadine, intravenous, intramuscular, subcutaneous or oral dosage range from 5 mg/kg daily to 50 mg/kg daily;
- (b) clemastine, intravenous, intramuscular, subcutaneous or oral dosage range from 20 mg/kg daily to 200 mg/kg daily;
- (c) setastine, intravenous, intramuscular or subcutaneous dosage range from 20 mg/kg daily to 200 mg/kg daily;
- (d) indomethacin, intravenous, intramuscular, subcutaneous or oral dosage range from 1 mg/kg daily to 100 mg/kg daily;
- (e) piroxicam, intravenous, intramuscular, subcutaneous or oral dosage range from 20 mg/kg daily to 200 mg/kg daily;
- (f) phenylbutazone, intravenous, intramuscular, subcutaneous or oral dosage range from 50 mg/kg daily to 500 mg/kg daily;
- (g) dexamethasone (Decadron, Merck & Co.), dosage range from 0.25 mg daily to 18 mg daily;
- (h) phenidone, intravenous, intramuscular, subcutaneous or oral dosage range from 25 mg/kg daily to 1 gm/kg daily;
- (i) nordihydroguaiaretic acid, intravenous, intramuscular, subcutaneous or oral dosage range from 100 mg/kg daily to 2 gm/kg daily;
- (j) ketoconazole, intravenous, intramuscular, subcutaneous or oral dosage range from 100 mg/kg daily to 2 gm/kg daily;
- (k) suprofen, dosage range from 5 mg/kg daily to 100 mg/kg daily;
- (l) ketoprofen, dosage range from 2 mg/kg daily to 50 mg/kg daily;
- (m) indoprofen, dosage range from 1 mg/kg daily to 30 mg/kg daily;
- (n) sudoxicam, dosage range from 0.5 mg/kg daily to 40 mg/kg daily;
- (o) naproxen, dosage range from 1 mg/kg daily to 100 mg/kg daily;
- (p) meclofenamic acid, dosage range from 15 mg/kg daily to 150 mg/kg daily;
- (q) ibuprofen, dosage range from 15 mg/kg daily to 150 mg/kg daily;

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- (r) diclofenac, dosage range from 1 mg/kg daily to 25 mg/kg;
 - (s) fenoprofen, dosage range from 5 mg/kg daily to 100 mg/kg daily;
 - (t) hydroxychloroquine, dosage range from 20 mg/kg daily to 400 mg/kg daily;
 - (u) 2,6-diamino-N-[[1-(1-oxotridecyl)-2-piperidinyl]-methyl]-hexanamide, dosage range from 0.5 mg/kg daily to 50 mg/kg daily;
 - (v) bucloxic acid, dosage range from 200 mg daily to 2 gm daily;
 - (w) butibufen, dosage range from 40 mg/kg daily to 400 mg/kg daily;
 - (x) carprofen, dosage range from 0.2 mg/kg daily to 50 mg/kg daily;
 - (y) the (S) (+) enantiomer of carprofen, dosage range from 50 mg daily to 750 mg daily;
 - (z) 6-(2,4-difluorophenoxy)-5-methylsulfonylamino-1-indanone (Ciba-Geigy AG), dosage range from 0.2 mg/kg daily to 20 mg/kg daily;
 - (a') loxoprofen, dosage range from 0.1 mg/kg daily to 25 mg/kg daily;
 - (b') diaveridine, dosage range from 25 mg/kg daily to 500 mg/kg daily;
 - (c') ditazol, dosage range from 25 mg/kg daily to 750 mg daily;
 - (d') droxicam, dosage range from 0.1 mg/kg daily to 50 mg/kg daily;
 - (e') (Z)-3-[4-(acetyloxy)-5-ethyl-3-methoxy-1-naphthalenyl]-2-methyl-2-propenoic acid, dosage range from 10 mg/kg daily to 500 mg/kg daily;
 - (f') ebselen, intravenous, intramuscular, subcutaneous or oral dosage range from 5 mg/kg daily to 500 mg/kg daily;
 - (g') 1-p-chlorobenzyl-2-dimethyl-aminomethylcyclohexen-1,2, dosage range from 2.5 mg/kg daily to 250 mg/kg daily;
 - (h') etoclofene, intravenous, intramuscular, subcutaneous or oral dosage range from 1 mg/kg daily to 400 mg/kg daily;
 - (i') flufenamic acid, dosage range from 1 mg/kg daily to 400 mg/kg daily;
 - (j') benzydamine, dosage range from 10 mg/kg daily to 1 gm/kg

daily;

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(l') mefenamic acid, dosage range from 1 mg/kg daily to 400 mg/kg daily;

(m') fenbufen, dosage range from 250 mg daily to 1.25 gm daily;

(n') felbinac, dosage range from 100 mg daily to 1.25 gm daily;

(o') fenclorac, dosage range from 0.5 mg/kg daily to 50 mg/kg daily;

(p') fenclozic acid, dosage range from 25 mg daily to 500 mg daily;

(q') fendosal, dosage range from 5 mg/kg daily to 200 mg/kg daily;

(r') isoxepac, dosage range from 200 mg daily to 2 gm daily;

(s') imidazole salicylate, dosage range from 50 μ mol/kg daily to 0.5 mmol/kg daily;

(t') isoxicam, dosage range from 50 mg daily to 500 mg daily;

(u') tolmetin, dosage range from 50 mg daily to 500 mg daily;

(v') leflunomide, dosage range from 50 μ g daily to 50 mg daily;

(w') isofezolac, dosage range from 0.1 mg/kg daily to 25 mg/kg daily;

(x') 1-isobutyl-3,4-diphenylpyrazole-5-acetic acid, dosage range from 0.5 mg/kg daily to 50 mg/kg daily;

(y') S-adenosylmethionine, dosage range from 500 mg daily to 10 gm daily;

(z') D-myo-inositol-1.2.6-trisphosphate, intravenous, intramuscular, subcutaneous or oral dosage range from 10 mg/kg daily to 1.5 gm daily;

(a'') diacetylrhein, dosage range from 10 mg daily to 500 mg daily;

(b'') cinmetacin, dosage range from 2 mg/kg daily to 400 mg/kg daily;

(c'') tinoridine, dosage range from 2.5 mg/kg daily to 250 mg/kg daily;

(d'') nimesulide, dosage range from 100 mg daily to 2 gm daily;

(e'') prenazone, dosage range from 0.5 mg/kg daily to 400 mg/kg daily;

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(f'') naphthypramide, dosage range from 0.5 mg/kg daily to 400 mg/kg daily;

(g'') perisoxal, dosage range from 0.5 mg/kg daily to 400 mg/kg daily;

(h'') proquazone, dosage range from 150 mg daily to 1.5 gm daily;

(i'') ketorolac, dosage range from 20 µg/kg daily to 2 mg/kg daily;

(j'') hydrocortisone (Hydrocortone, Merck & Co.), dosage range from 1 mg daily to 400 mg daily;

(k'') prednisolone (Pediapred, Fisons), dosage range from 1 mg daily or every other day to 250 mg daily;

(l'') cortisone (Cortone, Merck & Co.), dosage range from 5 mg daily to 400 mg daily;

(m'') prednisone (Deltasone, Upjohn), dosage range from 1 mg daily to 250 mg daily, or alternate day dosing;

(n'') methylprednisolone (Medrol, Upjohn), dosage range from 1 mg daily to 250 mg daily, or alternate day dosing;

(o'') methylprednisolone acetate (Depo-Medrol, Upjohn), intra-synovial, intralesional or intramuscular dosage range from 0.5 mg daily to 50 mg daily, or weekly dosage of from 20 mg to 120 mg;

(p'') triamcinolone (Aristocort, Fujisawa), dosage range from 1 mg daily to 200 mg daily, or alternate day dosing;

(q'') triamcinolone diacetate (Aristocort suspensions, Fujisawa), intramuscular, intrasynovial or intralesional dosage range from 1 mg daily to 200 mg daily, or alternate day dosing;

(r'') betamethasone (Celestone, Schering), dosage range from 0.2 mg daily to 12 mg daily, or alternate day dosing;

(s'') betamethasone (Celestone Soluspan suspension, Schering), intramuscular or intralesional dosage range from 0.1 mg daily to 10 mg daily, or alternate day dosing;

(t'') dexamethasone (Decadron phosphate injection, Merck & Co.), intramuscular, intravenous or intralesional dosage range from 0.1 mg daily to 10 mg daily;

(u'') cortisone (Cortone suspension, Merck & Co.), intramuscular dosage range from 5 mg daily to 400 mg daily;

(v'') hydrocortisone (Hydrocortone phosphate injection, Merck

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& Co.), intramuscular, intravenous or subcutaneous dosage range from 1 mg daily to 400 mg daily;

(w'') prednisolone (Hydeltrasol injection, Merck & Co.), intravenous, intramuscular, intra-articular, intralesional and soft tissue dosage range from 1 mg daily to 100 mg daily; and (x'') *N,N'*-diphenyl-*p*-phenylenediamine, dosage range from 10 mg/kg daily to 250 mg/kg daily.

The following illustrate specific formulations according to the present invention.

4-guanidinocyclohexanecarboxylic acid	1 gm
<i>N</i> -acetylcysteine	750 mg
cypheptadine	300 mg
<i>p</i> -aminobenzoic acid, potassium salt	15 gm
ebselen	20 gm
<i>S</i> -adenosylmethionine	10 gm
4-(aminoguanidino)-2-methoxybenzoic acid	5 gm
deferroxamine mesylate	500 mg
meclofenamic acid	5 gm

Example 22

Clinical treatment of post-event acute central nervous system trauma, including stroke and spinal cord trauma can be improved by use of a composition comprising from about 1 gm to about 20 gm of at least one primary therapeutic agent comprising a primary amine benzoic acid derivative having a molecular weight of from about 100 to about 1,400 Daltons, and optionally at least one substance selected from those noted above in section (v) through section (ix), and a medicament recognized as effective to treat post-event acute central nervous system trauma, including stroke and spinal cord trauma, such as, for example,

(a) heparin calcium (Calciparine, Du Pont Multi-Source), intravenous or subcutaneous dosage range from 5,000 units daily to 40,000 units daily;

(b) heparin sodium (Heparin Lock Flush solution, Wyeth-Ayerst Laboratories), intravenous or subcutaneous dosage range from

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- 5,000 units daily to 40,000 units daily;
- (c) warfarin (Coumadin, Du Pont), dosage range from 1 mg daily to 15 mg daily;
- (d) ticlopidine (Ticlid, Syntex), dosage range from 50 mg daily to 750 mg daily;
- (e) aminophylline, intramuscular, intravenous, subcutaneous or oral dosage range from 5 mg/kg daily to 75 mg/kg daily;
- (f) isoproterenol (Isuprel, Sanofi Winthrop), intravenous, intramuscular or subcutaneous dosage range from 10 µg daily to 1 mg daily;
- (g) methohexital sodium, intravenous dosage range from 5 mg/kg/hr to 50/kg/hr post-trauma;
- (h) tirilazad mesylate (U-74006F), intravenous dosage range from 150 µg/kg/hr to 15 mg/kg/hr;
- (i) derivative of tirilazad in which the steroid portion of the chemical structure has been replaced with the tetramethyl chroman portion of d-α tocopherol (U78517F, Upjohn), intravenous dosage range from 150 µg/kg/hr to 15 mg/kg/hr;
- (j) allopurinol (Zyloprim, Burroughs Wellcome), dosage range from 50 mg daily to 800 mg daily;
- (k) ebselen, intravenous, intramuscular, subcutaneous or oral dosage range from 5 mg/kg daily to 500 mg/kg daily; and
- (l) methylprednisolone, maintenance intravenous, intramuscular, subcutaneous or oral dosage range from 5 µg/kg daily to 0.1 mg/kg daily or immediate post-event treatment intravenous, intramuscular or subcutaneous dosage range from 30 mg/kg to 160 mg/kg during a 24 hour period;
- (m) aspirin, dosage range from 50 mg daily to 1.3 gm daily;
- (n) sulfinpyrazone (Anturane, CIBA), dosage range from 50 mg daily to 800 mg daily;
- (o) dipyridamole (Persantine, Boehringer Ingelheim), dosage range from 25 mg daily to 400 mg daily;
- (p) clofibrate (Atromid-S, Wyeth-Ayerst Laboratories), dosage range from 100 mg daily to 2 gm daily;
- (q) tissue plasminogen activator (Activase, Genentech), intravenous dosage range from 5 mg daily to 150 mg daily;
- (r) streptokinase (Streptase, Astra), intravenous dosage range from 50,000 IU daily to 500,000 IU daily; and
- (s) N-methyl-D-aspartate glutamate receptor antagonists ad-

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ministered orally, intramuscularly, subcutaneously or intravenously such as

trihexyphenidyl (Artane, Lederle), dosage range from 0.1 mg daily to 20 mg daily;

ethopropazine (Paridol), dosage range from 10 mg daily to 400 mg daily;

procyclidine (Kemadrin, Burroughs Wellcome), dosage range from 1 mg daily to 40 mg daily;

diphenhydramine (Benadryl, Parke-Davis), dosage range from 5 mg daily to 200 mg daily;

dizocilpine (Neurogard, Merck Sharp & Dohme), dosage range from 0.1 μ g/kg daily to 10 mg/kg daily;

amantadine (Symmetrel, Du Pont Multi-Source Products), dosage range from 10 mg daily to 400 mg daily;

memantine, dosage range from 10 mg daily to 400 mg daily;

milacemide, dosage range from 50 mg daily to 2.5 grams daily;

and

dextrorphan (Roche), dosage range from 10 mg daily to 400 mg daily;

(t) low molecular weight sulphate/dermatan sulphate glyco-amino-glycan heparinoid mixtures, 6,500 Dalton mean molecular weight, intravenous, intramuscular or subcutaneous dosage range from 250 anti-factor-Xa units daily to 10,000 anti-factor-Xa units daily; and

(u) moclobemide (Aurorix, Hoffmann-La Roche), dosage range from 50 mg daily to 600 mg daily.

The following illustrate specific formulations according to the present invention.

4-aminocyclohexanecarboxylic acid	1 gm
deferoxamine mesylate	500 mg
heparin calcium	5,000 units
p-aminobenzoic acid	15 gm
d- α -tocopheryl succinate	3,500 I.U.
ebselen	20 gm
methylprednisolone	5 mg
4-aminophenylacetic acid	5 gm

NO 351174
ebselen
moclobemide

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10 gm
250 mg

Example 23

Clinical treatment of post-event consequences of kidney ischemia and reperfusion can be improved by use of a composition comprising from about 1 gm to about 20 gm of at least one primary therapeutic agent comprising a primary amine benzoic acid derivative having a molecular weight of from about 100 to about 1,400 Daltons, and optionally at least one substance selected from those noted above in section (v) through section (ix), and a medicament recognized as effective to treat post-event consequences of kidney ischemia and reperfusion, such as, for example,

- (a) trimetazidine, dosage range from 100 µg/kg daily to 3.0 mg/kg daily;
- (b) allopurinol (Zyloprim, Burroughs Wellcome), dosage range from 50 mg daily to 800 mg daily;
- (c) bucloxic acid, dosage range from 200 mg daily to 2 gm daily;
- (d) indometacin, dosage range from 25 mg daily to 300 mg daily;
- (e) ebselen, dosage range from 5 mg/kg daily to 1 gm/kg daily;
- (f) methylprednisolone (Medrol, Upjohn), dosage range from 1 mg daily to 250 mg daily, or alternate day dosing;
- (g) methylprednisolone (Solu Medrol, Upjohn), intramuscular or intravenous dosage range from 0.25 mg/kg daily to 3 mg/kg daily;
- (h) prednisone (Deltasone, Upjohn), dosage range from 1 mg daily to 250 mg daily, or alternate day dosing;
- (i) cyclophosphamide (Cytosan, Bristol-Myers Oncology), dosage range from 0.1 mg/kg daily to 5 mg/kg daily;
- (j) cyclophosphamide (Cytosan for injection, Bristol-Myers Oncology), intravenous, intramuscular or subcutaneous dosage range from 0.1 mg/kg daily to 5 mg/kg daily, 2 mg/kg to 5 mg/kg twice weekly or 10 mg/kg to 15 mg/kg every seven to ten days;
- (k) chlorambucil (Leukeran, Burroughs Wellcome), dosage range

from 0.5 mg daily to 10 mg daily^{///};

(l) cyclosporin A (Sandimmune, Sandoz Pharmaceutical), dosage range from 1 mg/kg daily to 15 mg/kg daily;

(m) azathioprine (Imuran, Burroughs Wellcome), dosage range from 0.1 mg/kg daily to 2.5 mg/kg daily; and

(n) *N,N'*-diphenyl-*p*-phenylenediamine, dosage range from 10 mg/kg daily to 250 mg/kg daily.

The following illustrate specific formulations according to the present invention.

4-amino-2-hydroxyphenylacetic acid	1 gm
nordihydroguaiaretic acid	5 gm
trimetazidine	7.5 mg
 p-aminobenzoic acid	 15 gm
mixed tocopherols	3,500 I.U.
<i>N,N'</i> -diphenyl- <i>p</i> -phenylenediamine	15 gm
 4-(aminoguanidino)phenylacetic acid	 5 gm
D-myo-inositol-1.2.6-trisphosphate	20 gm
ebselen	5 gm
cyclophosphamide	200 mg

Example 24

Clinical treatment of post-event consequences of reperfusion subsequent to myocardial infarction can be improved by use of a composition comprising from about 1 gm to about 20 gm of at least one primary therapeutic agent comprising a primary amine benzoic acid derivative having a molecular weight of from about 100 to about 1,400 Daltons, and optionally at least one substance selected from those noted above in section (v) through section (ix), and a medicament recognized as effective to treat post-event consequences of reperfusion subsequent to myocardial infarction, such as, for example,

(a) trimetazidine, dosage range from 100 ug/kg daily to 3.0 mg/kg daily;

(b) allopurinol (Zyloprim, Burroughs Wellcome), dosage range from 50 mg daily to 800 mg daily;

(c) lidocaine (*Lignocainum*, Polfa), intravenous, subcutaneous

or intramuscular dosage range from 0.5 mg/kg to 1 mg/kg until ectopy resolves, followed by intravenous continuous infusion at a rate of from 20 μ g/kg/min to 50 μ g/kg/min;

(d) procainamide (Procan SR extended-release tablets, Parke-Davis), dosage range from 200 mg daily to 5 gm daily;

(e) β -adrenoceptor blockers such as acebutolol (Sectral), dosage range from 20 mg daily to 1.2 gm daily;

alprenolol, dosage range from 0.5 mg/kg daily to 5 mg/kg daily;

atenolol (Tenormin), dosage range from 2.5 mg daily to 200 mg daily;

betaxolol (Kerlone), dosage range from 1 mg daily to 20 mg daily;

carteolol (Cartrol), dosage range from 0.25 mg daily to 10 mg daily;

esmolol (Brevibloc, Du Pont Pharmaceuticals), intravenous dosage range from 50 μ g/kg/min to 0.2 mg/kg/min;

labetalol (Normodyne), dosage range from 20 mg daily to 1.8 gm daily;

metoprolol (Lopressor), dosage range from 5 mg daily to 200 mg daily;

nadolol (Corgard), dosage range from 4 mg daily to 240 mg daily;

oxprenolol, dosage range from 0.5 mg/kg daily to 5 mg/kg daily;

penbutolol (LevatoI), dosage range from 2 mg daily to 80 mg daily;

pindolol (Visken), dosage range from 0.5 mg daily to 60 mg daily;

propranolol (Inderal or Inderal LA), dosage range from 4 mg daily to 320 mg daily;

sotalol (Betapace, Berlex), dosage range from 30 mg daily to 320 mg daily; and

timolol (Blocadren), dosage range from 1 mg daily to 60 mg daily;

(f) nitrates such as

sodium nitroprusside, intravenous dosage range from 1 mg daily to 100 mg daily;

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million I.U. over one hour;

acylated streptokinase-plasmincomplex (anistreplase), intravenous dosage range from 3 I.U. to 30 I.U. over two minutes; and

recombinant tissue plasminogen activator (alteplase, rt-PA), intravenous dosage range from 10 mg to 100 mg over a four hour period;

(n) heparin, intravenous or subcutaneous dosage range 10,000 units/day to 25,000 units/day;

(o) aspirin, dosage range from 50 mg daily to 1.5 gm daily;

(p) angiotensin converting enzyme inhibitors including captopril (Capoten), dosage range from 2.5 mg daily to 300 mg daily;

enalapril (Vasotec), dosage range from 0.25 mg daily to 40 mg daily;

fosinopril (Monopril), dosage range from 1 mg daily to 60 mg daily;

lisinopril (Zestril), dosage range from 0.5 mg daily to 40 mg daily;

ramipril (Altace), dosage range from 0.25 mg daily to 10 mg daily;

quinapril (Accupril, Parke-Davis), dosage range from 1 mg daily to 80 mg daily;

quinapril/hydrochlorothiazide combinations (Accuretic, Parke-Davis), dosage range from 2 mg quinapril and 1.25 mg hydrochlorothiazide daily to 80 mg quinapril and 125 mg hydrochlorothiazide daily; and

benazepril (Lotensin, CIBA Pharmaceutical), dosage range from 0.1 mg daily to 80 mg daily.

The following illustrate specific formulations according to the present invention.

4-amino-2-methoxyphenylacetic acid	1 gm
butylated-hydroxytoluene	200 mg
allopurinol	200 mg
 p-aminobenzoic acid	 20 gm

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tert-butylhydroquinone	1 gm
isosorbide 5-mononitrate	100 mg
4-aminophenylacetic acid	10 gm
2,6-di-tert-butyl-4-[2'-thenoyl]phenol	500 mg
captopril	200 mg

Example 25

Use of agents previously recognized as having general anti-inflammatory properties and as possibly having usefulness in clinically treating chronic inflammatory diseases of varying origin, but which at present remain under investigation can be improved by use of a composition comprising from about 1 gm to about 20 gm of at least one primary therapeutic agent comprising a primary amine benzoic acid derivative having a molecular weight of from about 100 to about 1,400 Daltons, and optionally at least one substance selected from those noted above in section (v) through section (ix), and an agent previously recognized as having general anti-inflammatory properties and as possibly having usefulness in clinically treating chronic inflammatory diseases of varying origin, but which at present remain under investigation, such as, for example,

- (a) tilomisolet (WY-18,251, NSC-310,663), dosage range from 0.1 mg/kg daily to 100 mg/kg daily;
- (b) tenidap, dosage range from 0.1 mg/kg daily to 100 mg/kg daily;
- (c) 1-[(4-chlorophenyl)methyl]-2-methyl-5-(quinolinylmethoxy)-1H-indole-3-acetic acid, dosage range from 0.1 mg/kg daily to 100 mg/kg daily;
- (d) tepoxalin, dosage range from 0.1 mg/kg daily to 100 mg/kg daily;
- (e) scalaradial, dosage range from 0.1 mg/kg daily to 100 mg/kg daily;
- (f) neutral macrolide of molecular formula $C_{44}H_{69}NO_{12} \cdot H_2O$ derived from Streptomyces tsukubaensis No. 9993 (FK506), dosage range from 0.5 mg/kg daily to 50 mg/kg daily;
- (g) tirilazad mesylate (U-74006F), intravenous dosage range from 0.15 mg/kg/hr to 15 mg/kg/hr;

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- (h) derivative of tirilazad in which the steroid portion of the chemical structure has been replaced with the tetramethyl chroman portion of d- α tocopherol (U78517F, Upjohn), intravenous dosage range from 150 μ g/kg/hr to 15 mg/kg/hr;
- (i) pentoxifylline (Hoechst-Roussel Pharmaceuticals), intravenous, intramuscular or subcutaneous dosage range from 1 mg/kg daily to 100 mg/kg;
- (j) indoxole, dosage range from 0.5 mg/kg daily to 50 mg/kg daily;
- (k) bimetopyrol, dosage range from 0.5 mg/kg daily to 50 mg/kg daily;
- (l) flumizole, dosage range from 0.5 mg/kg daily to 50 mg/kg daily;
- (m) phenidone, intravenous, intramuscular, subcutaneous or oral dosage range from 25 mg/kg daily to 1 gm/kg daily;
- (n) ebselen, intravenous, intramuscular, subcutaneous or oral dosage range from 5 mg/kg daily to 500 mg/kg daily;
- (o) bucolome, dosage range from 200 mg daily to 2 gm daily;
- (p) sodium 2-[4-(2-oxocyclopentylmethyl)phenyl]propionate dihydrate, dosage range from 0.1 mg/kg daily to 25 mg/kg daily;
- (q) sideritoflavone, dosage range from 50 mg/kg daily to 1 gm daily;
- (r) cirsiliol, dosage range from 50 mg/kg daily to 1 gm daily;
- (s) hypolaetin-8-glucoside, dosage range from 50 mg/kg daily to 1 gm daily;
- (t) hypolaetin, dosage range from 50 mg/kg daily to 1 gm daily;
- (u) oroxindin, dosage range from 50 mg/kg daily to 1 gm daily;
- (v) quercetagetin-7-glucoside, dosage range from 50 mg/kg daily to 1 gm daily;
- (w) gossypin, dosage range from 50 mg/kg daily to 1 gm daily;
- (x) hibifolin, dosage range from 50 mg/kg daily to 1 gm daily;
- (y) gossypetin, dosage range from 50 mg/kg daily to 1 gm daily;
- (z) leucocyanidol, dosage range from 50 mg/kg daily to 1 gm

daily;

(a') indoprofen, dosage range from 0.5 mg/kg daily to 50 mg/kg daily;

(b') crude extract of Mandevilla velutina, dosage range from 50 mg/kg daily to 1 gm/kg daily;

(c') 1-[3-(naphth-2-ylmethoxy)phenyl]-1-(thiazol-2-yl)propyl methyl ether, dosage range from 1 mg/kg daily to 100 mg/kg daily;

(d') epirizole, dosage range from 5 mg/kg daily to 150 mg/kg daily;

(e') DL-2-(4-hexyloxyphenyl)glycine octyl ester, dosage range from 25 mg daily to 500 mg daily;

(f') DL-2-[4-(5.5-dimethylhexyloxy)phenyl]glycine octyl ester, dosage range from 25 mg daily to 500 mg daily;

(g') meloxicam, dosage range from 0.1 mg/kg daily to 50 mg/kg daily;

(h') kojic acid, dosage range from 0.1 mg/kg daily to 50 mg/kg daily;

(i') 2-(2-hydroxy-4-methylphenyl)aminothiazolehydrochloride, dosage range from 0.1 mg/kg daily to 50 mg/kg daily;

(j') 2-(p-bromophenyl)-9-dimethylaminopropyl-9H-imidazo[1,2- α]-benzimidazole, dosage range from 0.1 mg/kg daily to 50 mg/kg daily;

(k') benoxaprofen, dosage range from 0.1 mg/kg daily to 50 mg/kg daily;

(l') flunoxaprofen, dosage range from 0.1 mg/kg daily to 50 mg/kg daily;

(m') emorfazone, dosage range from 0.1 mg/kg daily to 100 mg/kg daily;

(n') misoprostol, dosage range from 10 μ g/k daily to 1 mg/kg daily;

(o') 6-methoxy-2-naphthylacetic acid, dosage range from 1 mg/kg daily to 100 mg/kg daily;

(p') niflumic acid, dosage range from 250 mg daily to 5 gm daily;

(q') clidanac, dosage range from 0.1 mg/kg daily to 100 mg/kg daily;

(r') proglumetacin, dosage range from 0.5 mg/kg daily to 200 mg/kg daily;

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(s') 4-(2-chlorophenyl)-2-[2-(4-isobutylphenyl)ethyl]-6,9-dimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3a][1,4]diazepine (Y-24180), dosage range from 10 μ g/kg daily to 10 mg/kg daily;

(t') paramethasone, intramuscular, intrasynovial, intralesional or oral dosage range from 1 mg daily to 200 mg daily, or alternate day dosing;

(u') paramethasone 21-acetate, intramuscular, intrasynovial, intralesional or oral dosage range from 1 mg daily to 200 mg daily, or alternate day dosing; and

(v') paramethasone disodium phosphate, intramuscular, intrasynovial, intralesional or oral dosage range from 1 mg daily to 200 mg daily, or alternate day dosing.

The following illustrate specific formulations according to the present invention.

4-aminophenylacetic acid, potassium salt	1 gm
N-acetylcysteine	1 gm
tenidap	10 mg

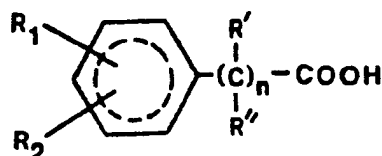
4-amino-2-methoxybenzoic acid	20 gm
d- α -tocopheryl succinate	3,000 I.U.
neutral macrolide of molecular formula	
C ₄₄ H ₆₉ NO ₁₂ ·H ₂ O derived from	
<u>Streptomyces tsukubaensis</u>	
No. 9993 (FK506)	3.5 gm

4-aminophenylacetic acid	15 gm
probucol	600 mg
tilomisolet	2 gm

Without further elaboration the foregoing will so fully illustrate my invention that others may, by applying current or future knowledge, adapt the same for use under various conditions of service.

I claim:

1. A method of treating a chronic inflammatory disease resulting from hypoxia/reperfusion site trauma; said disease or pathophysiologically related symptomology characterized in part by increased levels of lipid peroxidation and increased levels of resultant carbonyl compounds, said resultant carbonyl compounds constituting a toxic group of substances which additionally contribute to the continuation of the chronic inflammatory disease or pathophysiologically related symptomology; said method comprising systemic administration of a composition comprising (1) a therapeutically effective amount of a water soluble compound having a molecular weight of from about 100 to about 1,400 Daltons of the formula



wherein R_1 is $-\text{NH}_2$; $-\text{aminoalkyl}$ having 1-10 carbons; $-\text{NHC}(=\text{NH})\text{NH}_2$; $-(\text{CH}_2)_n\text{NHC}(=\text{NH})\text{NH}_2$ wherein n is 1-10; $\text{C}(=\text{NH})\text{NH}_2$; $-(\text{CH}_2)_n\text{---CH=NC}(=\text{NH})\text{NH}_2$ wherein n is 1-10; $-\text{NHC}(=\text{NH})\text{NHNH}_2$; $-(\text{CH}_2)_n\text{NHC}(=\text{NH})\text{NHNH}_2$ wherein n is 1-10; $-(\text{CH}_2)_n\text{---CH=NC}(=\text{NH})\text{NHNH}_2$ wherein n is 1-10; $-\text{NHNHC}(=\text{NH})\text{NH}_2$; $-(\text{CH}_2)_n\text{---NHNHC}(=\text{NH})\text{NH}_2$ wherein n is 1-10; and $-(\text{CH}_2)_n\text{---CH=N---NHC}(=\text{NH})\text{NH}_2$ wherein n is 1-10;

R_2 is H ; $-\text{OH}$; $-\text{O---CH}_3$; $-\text{O---R}'$ wherein R' is alkyl of 2-10 carbons; aminoalkyl wherein the alkyl group is 1-10 carbons; $-\text{SO}_3\text{H}$; $-\text{CH}_3$; and $-(\text{CH}_2)_n\text{CH}_3$ wherein n is 1-10;

R' and R'' are $-\text{H}$, OH or CH_3 ; and n is 0 or 1,

and the pharmaceutically acceptable salts, amide and ester derivatives thereof; (2) optionally an effective amount of at least one co-agent selected from the group consisting of (a) an anti-oxidant, a free radical trapping compound, a chemical having indirect anti-oxidant properties, a vitamin, a chemical conjugating substance which facilitates kidney drug elimina-

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tion, a metabolite at risk of depletion, a sulfhydryl containing chemical and a chemical which may act so as to facilitate glutathione activity and/or (b) a nonabsorbable polyamine substance, said nonabsorbable co-agent acting to covalently bind and sequester dietary carbonyl-containing products and (3) at least one medicament in an amount effective to treat said chronic inflammatory disease.

2. A method of treatment according to Claim 1 wherein the medicament recognized as effective is selected from the group consisting of a neuroactive drug; a vasoactive drug; a vascular relaxant; an immunoregulatory drug; an antibiotic; a thromboinhibitory drug; an antihistaminic drug; or a chemical selected from the group consisting of allopurinol, anthralin, 2-(p-bromophenyl)-9-dimethylamino-propyl-9H-imidazo[1,2- α]benzimidazole, 4H-2-carboxamido-4-phenylthieno-[3,2-c]-[1]-benzopyran, clofibrate, codeine, Mandevilla velutina, cysteamine, deodorized opium tincture, diphenoxylate, ephedrine and derivatives thereof, estrogen, etretinate, flumizole, gabapentin, ganglioside GM₁, isoniazid, isotretinoin, lidocaine, linopirdine, loperamide, memantine, methoxsalen, mixed cow brain gangliosides, myelin, 4H-4-phenylthieno-[3,2-c]-[1]-benzopyran-2-carboxylic acid, procainamide, pyridoxine and pharmaceutically acceptable derivatives thereof, sulfinpyrazone, taurine, tiapride and zileuton.

3. The method of Claim 1 wherein said chronic inflammatory disease is selected from the group consisting of: chronic gingivitis; chronic periodontitis; chronic autoimmune gastritis; ileitis; inflammatory bowel disease; interstitial cystitis; psoriasis; various forms of arthritis; tendinitis; carpal tunnel syndrome and other cumulative trauma disorders; systemic and chronic discoid lupus erythematosus; pneumoconiosis; chronic obstructive pulmonary disease; inflammatory myopathies; epilepsy; inflammatory neuropathies; Alzheimer's disease; myasthenia gravis; multiple sclerosis; inflammatory site edema; and post-event hypoxia/reperfusion tissue damage subsequent to acute central nervous system trauma, stroke, kidney ischemia or myocardial infarction.

4. The method of Claim 1 wherein said therapeutically effective amount of said at least one primary agent is a

dosage in the range of from 600 mg to about 20 gm per day in one or more divided doses, preferably from about 1 gm to about 20 gm per day, more preferably from about 3 gm to about 20 gm per day, and most preferably from about 6 gm to about 20 gm per day.

5. The method of Claim 1 wherein said therapeutically effective amount of said at least one primary agent is a dosage in the range of 15 mg/kg daily to about 800 mg/kg daily, preferably 30 mg/kg daily to about 800 mg/kg, more preferably 60 mg/kg daily to about 800mg/kg, and most preferably 120 mg/kg daily to about 800 mg/kg.

6. The method of Claim 1 wherein the composition is administered orally.

7. The method of Claim 1 wherein said therapeutically effective amount of the at least one primary therapeutic agent is administered intravenously, intramuscularly or subcutaneously.

8. The method of Claim 1 wherein the nonabsorbable co-agent is selected from the group consisting of:

a. naturally occurring polysaccharides having β -1,2, β -1,3, β -1,4 and/or β -1,6 linkages containing aminosugars including the chitin class of biopolymers having the general structure of poly- β -(1->4)-N-acetyl-D-glucosamine, and bearing at least one free primary amine group;

b. deacetylated naturally occurring polysaccharides, having at least one N-acetylated residue, wherein upon chemical deacetylation thereof, said deacetylated naturally occurring polysaccharide is a high molecular weight derivative bearing primary amine groups directly linked to sugar carbons; including chitosan but not limited to chitosan;

c. chemically aminated polysaccharides from the group consisting of:

aminodeoxy polysaccharides such as 2-amino-2-deoxy-cellulose; aminoalkyl-, amino(hydroxyalkyl)-, aminoalkyl-ether-, and amino(hydroxyalkyl)-ether- derivatives of cellulose, chitin and other naturally occurring non-digestible carbohydrates selected from the group consisting of

$H_2N-(CH_2)_n$ -[carbohydrate] where $n = 1-10$, including alkyl isomers;

$H_2N-(CH_2)_m$ -CHOH-(CH₂)_n-[carbohydrate], where $m = 0-10$ and

$n = 0-10$;

$H_2N-(CH_2)_n-O-[carbohydrate]$ where $n = 1-10$;

$H_2N-(CH_2)_n-CHOH-(CH_2)_m-O-[carbohydrate]$ where $m = 0-10$

and $n = 0-10$;

aminobenzyl- derivatives of cellulose, chitin or other naturally occurring non-digestible carbohydrates selected from the group consisting of

$H_2N-C_6H_4-(CH_2)_n-[carbohydrate]$;

$H_2N-CH_2-C_6H_4-(CH_2)_n-[carbohydrate]$;

$H_2N-C_6H_4-(CH_2)_n-O-[carbohydrate]$ where $n = 0 - 10$, and

$H_2N-C_6H_4-(CH_2)_n-CHOH-(CH_2)_m-O-[carbohydrate]$ where $m = 0-10$

and $n = 0-10$, including p-, o- and m-benzene ring amino-isomers, aminomethyl- isomers and alkyl group isomers thereof;

guanidine and aminoguanidine derivatives of cellulose, chitin or other naturally occurring non-absorbable carbohydrates selected from the group consisting of:

$H_2N-C(=NH)-[carbohydrate]$;

$H_2N-C(=NH)-(CH_2)_n-[carbohydrate]$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$H_2N-C(=NH)-O-(CH_2)_n-[carbohydrate]$, where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$H_2N-C(=NH)-NH-[carbohydrate]$;

$H_2N-C(=NH)-NH-(CH_2)_n-[carbohydrate]$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$H_2N-C(=NH)-NH-(CH_2)_n-O-[carbohydrate]$, where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$H_2N-C(=NH)-N=CH-(CH_2)_n-[carbohydrate]$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$H_2N-C(=NH)-N=CH-(CH_2)_n-O-[carbohydrate]$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$H_2N-NHC(=NH)-NH-[carbohydrate]$;

$H_2N-NHC(=NH)-NH-(CH_2)_n-[carbohydrate]$, where $n = 1-10$, in-

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cluding hydrocarbon isomers and hydroxylated derivatives thereof;

$H_2N-NHC(=NH)-NH-(CH_2)_n-O-[carbohydrate]$, where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$H_2N-NHC(=NH)-N=CH-(CH_2)_n-[carbohydrate]$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$H_2N-NHC(=NH)-N=CH-(CH_2)_n-O-[carbohydrate]$, where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$H_2N-C(=NH)-NH-NH-[carbohydrate]$;

$H_2N-C(=NH)-NH-NH-(CH_2)_n-[carbohydrate]$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$H_2N-C(=NH)-NH-NH-(CH_2)_n-O-[carbohydrate]$, where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$H_2N-C(=NH)-NH-N=CH-(CH_2)_n-[carbohydrate]$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$H_2N-C(=NH)-NH-N=CH-(CH_2)_n-O-[carbohydrate]$, where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

d. primary amine, aminoguanidine and guanidine derivatives of sucrose polyesters having one or more carbonyl trapping functional group per molecule wherein each carbonyl trapping functional group is in the ω -, $\omega-1$ or other isomeric position within the fatty acyl chains, wherein each fatty acyl chain may have from 3 to 26 carbons, from one to five nitrogen functional groups and from one to 24 hydroxyl groups;

e. synthetic polysaccharides consisting partly or entirely of aminosugars bound by $\beta-1,2$, $\beta-1,3$, $\beta-1,4$ and/or $\beta-1,6$ linkages;

f. mixed polysaccharide polymeric derivatives wherein primary amine, aminoalkyl (one to ten carbons per alkyl group), amino-hydroxyalkyl (one to ten carbons per alkyl group and one to ten hydroxyl groups per alkyl group), aminoguanidine, aminoguanidiny-alkyl (one to ten carbons per alkyl group),

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aminoalkylguanidiny (one to ten carbons per alkyl group), guanidine, aminobenzene and/or aminoalkylbenzene (one to ten carbons per alkyl group) functional groups are covalently attached to matrices such as epi-chlorohydrin copolymers of cellulose or chitin and wherein hydrocarbon spacer groups may include alkene as well as alkyl groups; and

g. non-polysaccharide polymeric derivatives wherein primary amine, aminoalkyl (one to ten carbons per alkyl group), amino-hydroxyalkyl (one to ten carbons per alkyl group and one to ten hydroxyl groups per alkyl group), aminoguanidine, aminoguanidiny-alkyl (one to ten carbons per alkyl group), aminoalkylguanidiny (one to ten carbons per alkyl group), guanidine, aminobenzene and/or aminoalkylbenzene (one to ten carbons per alkyl group) functional groups are covalently attached to a synthetic non-digestible polymer selected from the group consisting of polystyrene, styrene-divinylbenzene copolymer, polyvinyl alcohol and crosslinked derivatives thereof, and wherein hydrocarbon spacer groups may include alkene as well as alkyl groups.

9. The method of Claim 8 wherein said nonabsorbable polyamine is in a microfibrillated form or microcrystalline form having enhanced surface area, increased porosity, increased water retention capacity and enhanced chemical accessibility.

10. The method of Claim 8 wherein said therapeutically effective amount of said nonabsorbable polyamine is a dosage in the range of from 600 mg to about 20 gm per day in one or more divided doses, preferably from about 1 gm to about 20 gm per day, more preferably from about 3 gm to about 20 gm per day, and most preferably from about 6 gm to about 20 gm per day.

11. The method of Claim 8 wherein said therapeutically effective amount of said nonabsorbable polyamine is a dosage in the range of 15 mg/kg daily to about 800 mg/kg daily, preferably 30 mg/kg daily to about 800 mg/kg, more preferably 60 mg/kg daily to about 800mg/kg, and most preferably 120 mg/kg daily to about 800 mg/kg.

12. The method of Claim 1 wherein said co-agent is selected from the group consisting of

a) at least one anti-oxidant and free radical trapping

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compound selected from the group consisting of vitamin E derivatives such as α -tocopherol, β -tocopherol, γ -tocopherol, δ -tocopherol, ϵ -tocopherol, ζ_1 -tocopherol, ζ_2 -tocopherol and η -tocopherol, as well as ester derivatives thereof such as the corresponding acetate, succinate and nicotinate forms; β -carotene; vitamin A; butylated hydroxytoluene; butylated hydroxyanisole; propyl gallate; dodecylgallate; tert-butylhydroquinone; citric acid; ubiquinols; glutathione; homocysteine; methionine; dihydrolipoic acid; N-acetylcysteine; prostaglandin B₁ oligomers; 2-aminomethyl-4-tert-butyl-6-iodophenol; 2-aminomethyl-4-tert-butyl-6-propionylphenol; 2,6-di-tert-butyl-4-[2'-thenoyl]-phenol; N,N'-diphenyl-p-phenylenediamine; ethoxyquin; probucol; ebselen; 5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-3-(dimethylamino)-4-thiazolidinone; 5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-3-(methyl-amino)-4-thiazolidinone; D-myoinositol-1.2.6-trisphosphate; nor-dihydroguaiaretic acid; deferoxamine; tirilazad mesylate; derivative of tirilazad in which the steroid portion of the chemical structure has been replaced with the tetramethyl chroman portion of d- α tocopherol; trimetazidine; 2-(2-hydroxy-4-methylphenyl)aminothiazole hydrochloride; and N,N'-dimethylthiourea,

b) chemicals having indirect anti-oxidant properties selected from the group consisting of selenium and seleno-containing amino acids,

c) a vitamin selected from the group consisting of vitamin A; vitamin A aldehyde, also known as retinal; vitamin A acid, also known as retinoic acid; retinyl acetate; vitamin B₁, also known as thiamine; thiamine propyl disulfide; vitamin B₂, also known as riboflavin; riboflavin tetrabutrate; riboflavine 5'-phosphate ester monosodium salt; vitamin B₆, also known as pyridoxine; pyridoxal; pyridoxal HCl; pyridoxal 5-phosphate; pyridoxal 5-phosphate calcium salt; pyridoxamine; pyridoxamine dihydrochloride; pyridoxamine phosphate; vitamin B₁₂, also known as cyanocobalamin; methyl vitamin B₁₂, also known as co-methylcobalamin; vitamin D₂; vitamin D₃; vitamin D₄; vitamin H, also known as biotin; vitamin K₁; vitamin K₁ oxide; vitamins of the K₂ series; vitamin K₅; vitamin K₅

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hydrochloride; vitamin K₆; vitamin K₆ dihydrochloride; vitamin K₇; vitamin K₇ hydrochloride; vitamin K-S(II); vitamin L₁; vitamin L₂; vitamin U; methylmethioninesulfonium bromide; α -carotene; β -carotene; γ -carotene; ω -carotene; ψ -, ψ -carotene, also known as lycopene; 7,7',8,8',11,12-hexahydro- ψ -, ψ -carotene, also known as phytofluene; vitamin B₇, also known as carnitine; acetyl-L-carnitine; vitamin Bc, also known as folic acid; folinic acid; folinic acid calcium salt pentahydrate; niacinamide; nicotinic acid; nicotinic acid sodium salt sesquihydrate; nicotinic acid monoethanolamine salt; pantothenic acid; pantothenic acid sodium salt; and pantothenic acid calcium salt,

d) a chemical conjugating co-agent which facilitates kidney drug elimination selected from the group consisting of glycine and derivatives thereof,

e) a metabolite at risk of depletion selected from the group consisting of pantothenic acid and derivatives thereof,

f) a sulfhydryl containing substance or derivative thereof selected from the group consisting of homocysteine, acetylhomocysteine thiolactone, methionine or thiocetic acid, also known as α -lipoic acid, and

g) a chemical which may act so as to facilitate glutathione activity selected from the group consisting of as N-acetylcysteine; L-2-oxothiazolidine-4-carboxylate; timonacic; cysteamine; and lipoamide derivatives including malotilate, sulfarlem and oltipraz.

13. The method of Claim 1 wherein said at least one co-agent selected from group (2) is administered intravenously, intramuscularly or subcutaneously.

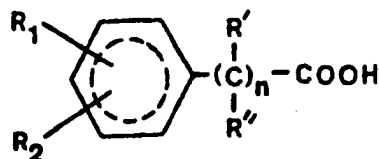
14. The method of Claim 1 wherein said medicament is administered intravenously, intramuscularly or subcutaneously.

15. A method of treating a mammal suffering from a chronic inflammatory disease characterized in part by increased lipid peroxidation and increased levels of resultant carbonyl compounds; wherein said disease is selected from the group consisting of gastrointestinal tract chronic inflammatory disorders, psoriasis, arthritis, inflammatory site edema, acute central nervous system trauma, stroke and myocardial

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infarction; said method comprising orally and/or intravenously administering a therapeutically effective amount of a composition of Claim 1.

16. A composition effective in treating by oral administration a chronic inflammatory disease, the composition comprising an effective amount of at least one carbonyl trapping therapeutic agent of the formula



wherein R_1 is $-\text{NH}_2$; $-\text{aminoalkyl}$ having 1-10 carbons; $-\text{NHC}(=\text{NH})\text{NH}_2$; $-(\text{CH}_2)_n\text{NHC}(=\text{NH})\text{NH}_2$ wherein n is 1-10; $\text{C}(=\text{NH})\text{NH}_2$; $-(\text{CH}_2)_n-\text{CH}=\text{NC}(=\text{NH})\text{NH}_2$ wherein n is 1-10; $-\text{NHC}(=\text{NH})\text{NHNH}_2$; $-(\text{CH}_2)_n\text{NHC}(=\text{NH})\text{NHNH}_2$ wherein n is 1-10; $-(\text{CH}_2)_n-\text{CH}=\text{NC}(=\text{NH})\text{NHNH}_2$ wherein n is 1-10; $-\text{NHNHC}(=\text{NH})\text{NH}_2$; $-(\text{CH}_2)_n-\text{NHNHC}(=\text{NH})\text{NH}_2$ wherein n is 1-10; and $-(\text{CH}_2)_n-\text{CH}=\text{N}-\text{NHC}(=\text{NH})\text{NH}_2$ wherein n is 1-10;

R_2 is H ; $-\text{OH}$; $-\text{O}-\text{CH}_3$; $-\text{O}-\text{R}'$ wherein R' is alkyl of 2-10 carbons; aminoalkyl wherein the alkyl group is 1-10 carbons; $-\text{SO}_3\text{H}$; $-\text{CH}_3$; and $-(\text{CH}_2)_n\text{CH}_3$ wherein n is 1-10;

R' and R'' are $-\text{H}$, $-\text{OH}$ or CH_3 ; and n is 0 or 1,

and an effective amount of at least one medicament selected from the group consisting of a neuroactive drug; a vasoactive drug; a vascular relaxant; an immunoregulatory drug; an antibiotic; a thromboinhibitory drug; an antihistaminic drug; and a chemical selected from the group consisting of allopurinol, anthralin, 2-(p-bromophenyl)-9-dimethylaminopropyl-9H-imidazo[1,2-b]-benzimidazole, 4H-2-carboxamido-4-phenylthieno-[3,2-c]-[1]-benzopyran, clofibrate, codeine, Mandevilla velutina, cysteamine, opium tincture, diphenoxylate, ephedrine and derivatives thereof, estrogen, etretinate, flumizole, gabapentin, isoniazid, isotretinoin, lidocaine, linopirdine, loperamide, memantine, methoxsalen, a cow brain ganglioside, myelin, 4H-4-phenylthieno-[3,2-c]-[1]-benzopyran-2-carboxylic acid, procainamide, pyridoxine and derivatives

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thereof, sulfinpyrazone, taurine, tiapride, and zileuton, wherein the carbonyl trapping therapeutic agent is present in an amount from 600 mg/day to about 20 gm/day.

17. The composition according to claim 16 wherein the neuroactive drug is a drug which affects acetylcholine synthesis, storage or release; an acetylcholine postreceptor agonist; an acetylcholinesterase inhibitor; a cholinergic drug; an anticholinergic drug; a skeletal muscle relaxant drug; an anxiolytic drug; an antidepressant drug; a monoamine oxidase inhibitor; a vasodilator or other nootropic direct brain metabolic enhancer drug; a neurotransmission enhancer drug; an antirage drug; an anticonvulsant drug; a N-methyl-D-aspartate glutamate receptor antagonist; an antipsychotic drug; or a serotonin reuptake inhibitor.

18. The composition according to claim 16 wherein the vasoactive drug is an angiotensin converting enzyme inhibitor; an antihypertensive drug; an alpha adrenergic blocker; a beta adrenergic blocker or a calcium channel blocker.

19. The composition according to claim 16 wherein the vascular relaxant is an antianginal drug, a coronary vasodilator drug or a bronchodilator drug.

20. The composition according to claim 16 wherein the immunoregulatory drug is a glucocorticosteroid; a nonsteroidal anti-inflammatory drug; an immunomodulator drug; an immunosuppressive drug; an interferon; an antimalarial drug or corticotropin.

21. The composition according to claim 16 wherein the antibiotic drug is an aminoglycoside antibiotic drug; an amphenicol antibiotic drug; an ansamycin antibiotic drug; a β -lactam antibiotic drug; a lincosamide antibiotic drug; a macrolide antibiotic drug; a polypeptide antibiotic drug; a tetracycline antibiotic drug; a β -lactamase inhibitor; an antiseptic; a surfactant; or a chemical selected from the group consisting of D-cycloserine, mupirocin, tuberlin and imipenem in combination with cilastatin sodium.

22. The composition according to claim 16 wherein the thromboinhibitory drug is an anticoagulant drug, an antithrombotic drug or a thrombolytic drug.

23. The composition of claim 16 additionally comprising an

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effective amount of at least one carbonyl trapping co-agent selected from the group consisting of a nonabsorbable primary amine polymer having at least one free primary amine group, an anti-oxidant, selenium and seleno-containing amino acids, a vitamin, a substance which facilitates glutathione biological activity, glycine and derivatives thereof which facilitate kidney drug elimination, a metabolite at risk of depletion, a sulfhydryl containing agent and derivatives thereof, and a free radical trapping substance.

24. The composition of Claim 16 together with a pharmaceutically acceptable carrier.

25. The composition of Claim 23 together with a pharmaceutically acceptable carrier.

26. A composition according to Claim 24 wherein the pharmaceutically acceptable carrier is an aqueous solution or suspension for injection, a comestible product for oral use, or a combination thereof.

27. A composition according to Claim 25 wherein the pharmaceutically acceptable carrier is an aqueous solution or suspension for injection, a comestible product for oral use, or a combination thereof.

28. A composition according to Claim 26 wherein the comestible product for oral use is a tablet for oral use, a sustained-release tablet or a foodstuff.

29. A composition according to Claim 27 wherein the comestible product for oral use is a tablet for oral use, a sustained-release tablet or a foodstuff.

30. The composition of Claim 16 for treating chronic gingivitis and/or chronic periodontitis wherein the medicament is selected from the group consisting of: a tetracycline; a surfactant; ebselen; a nonsteroidal anti-inflammatory drug; a glucocorticoid substance; a penicillin; a penicillin in combination with clavulanate potassium; a macrolide antibiotic substance; a cephalosporin; and a chemical selected from the group consisting of metronidazole, chlorhexidine, D-cycloserine, imipenem and imipenem optionally in combination with cilastatin sodium.

31. The composition of Claim 16 for treating chronic autoimmune gastritis wherein the medicament is selected from the

group consisting of: sodium ¹³⁰guaiazulene-3-sulfonate and ebselen.

32. The composition of Claim 16 for treating ileitis, including Crohn's disease wherein the medicament is selected from the group consisting of: sulfasalazine; dexamethasone, as well as pharmaceutically acceptable ester and salt derivatives thereof; methylprednisolone, as well as pharmaceutically acceptable ester and salt derivatives thereof; hydrocortisone, as well as pharmaceutically acceptable ester and salt derivatives thereof; metronidazole; ebselen; sustained-release formulations of 5-aminosalicylic acid; prednisolone, as well as pharmaceutically acceptable ester and salt derivatives thereof; cortisone, as well as pharmaceutically acceptable ester and salt derivatives thereof; prednisone, as well as pharmaceutically acceptable ester derivatives thereof; triamcinolone, as well as pharmaceutically acceptable ester and ether derivatives thereof; betamethasone, as well as pharmaceutically acceptable ester and salt derivatives thereof; diphenoxylate; diphenoxylate in combination with atropine sulfate; deodorized opium tincture; codeine; azathioprine; 6-mercaptopurine; cyclosporins A through I; and methotrexate.

33. The composition of Claim 16 for treating inflammatory bowel disease, including ulcerative colitis wherein the medicament is selected from the group consisting of: sulfasalazine; 5-amino-salicylic acid; 7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid; glutathione; zileuton; olsalazine; disodium azodisalicylate; dexamethasone, as well as pharmaceutically acceptable ester and salt derivatives thereof; eicosapentaenoic acid; salicylazosulfapyridine; sustained-release formulations of 5-aminosalicylic acid; diazo sulfanilamide ethylene polymer of 5-aminosalicylic acid; hydrocortisone, as well as pharmaceutically acceptable ester and salt derivatives thereof; prednisolone, as well as pharmaceutically acceptable ester and salt derivatives thereof; cortisone, as well as pharmaceutically acceptable ester and salt derivatives thereof; prednisone, as well as pharmaceutically acceptable ester derivatives thereof; methylprednisolone, as well as

pharmaceutically acceptable ester and salt derivatives thereof; triamcinolone, as well as pharmaceutically acceptable ester and ether derivatives thereof; betamethasone, as well as pharmaceutically acceptable ester and salt derivatives thereof; azathioprine; 6-mercaptopurine; diphenoxylate; deodorized opium tincture; codeine; loperamide; corticotropin; cyclosporins A through I; scopolamine; trihexyphenidyl; benztropine mesylate; procyclidine; biperiden; biperiden lactate; ethopropazine; propantheline bromide; and oxybutynin chloride.

34. The composition of Claim 16 for treating interstitial cystitis wherein the medicament is selected from the group consisting of: propantheline bromide; oxybutynin chloride; benztropine mesylate; trihexyphenidyl; procyclidine; biperiden; ethopropazine; scopolamine; benztropine mesylate; and biperiden lactate.

35. The composition of Claim 16 for treating psoriasis wherein the medicament is selected from the group consisting of: 7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid; eicosa-pentaenoic acid; dexamethasone, as well as pharmaceutically acceptable ester and salt derivatives thereof; methotrexate; hydrocortisone, as well as pharmaceutically acceptable ester and salt derivatives thereof; prednisolone, as well as pharmaceutically acceptable ester and salt derivatives thereof; cortisone, as well as pharmaceutically acceptable ester and salt derivatives thereof; prednisone, as well as pharmaceutically acceptable ester derivatives thereof; methylprednisolone, as well as pharmaceutically acceptable ester and salt derivatives thereof; triamcinolone, as well as pharmaceutically acceptable ester and ether derivatives thereof; betamethasone, as well as pharmaceutically acceptable ester and salt derivatives thereof; alclometasone 17,21-dipropionate; fluticasone propionate; mometasone 17-(2-furoate); clobetasol propionate; coal tar topical compositions; methoxsalen; etretinate; isotretinoin; anthralin; cyclosporins A through I; vitamin D₃, topically applied; and salicylic acid.

36. The composition of claim 16 for treating rheumatoid arthritis wherein the medicament is selected from the group consisting of: meclofenamic acid; mefenamic acid; flufenamic

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acid; amfenac; ethyl 2-amino-3-benzoylphenylacetate; diclofenac; etodolac; metiazinic acid; indomethacin; fenclozic acid; isofezolac; sulindac; tolmetin; glucametacin; cinmetacin; fenclofenac; fenbufen; butibufen; ketorolac tromethamine; tinoridine; fenoprofen; flurbiprofen; ibuprofen; ketoprofen; naproxen; bucloxic acid; the (S)(+) enantiomer of carprofen; phenylbutazone; oxyphenbutazone; feprazone; diflunisal; imidazole salicylate; sulfasalazine; benorylate; piroxicam; isoxicam; auranofin; aurothioglucose; gold sodium thiomalate; hydroxychloroquine; chloroquine; methotrexate; D-penicillamine; cyclophosphamide; prednisone, as well as pharmaceutically acceptable ester derivatives thereof; dexamethasone, as well as pharmaceutically acceptable ester and salt derivatives thereof; methylprednisolone, as well as pharmaceutically acceptable ester and salt derivatives thereof; (10-methoxy-4H-benzo[4,5]cyclo-hepta-[1,2-b]-thiophene-4-yliden)acetic acid; cyclosporins A through I; neutral macrolide of molecular formula $C_{44}H_{69}NO_{12} \cdot H_2O$ derived from Streptomyces tsukubaensis No. 9993; rapamycin; azathioprine; nabumetone; eicosapentaenoic acid; aloxiprin; azapropazone; fenopron; amiprilose; chlorambucil; aceclofenac; apocynin; capsaicin; 6-(2,4-difluorophenoxy)-5-methyl-sulfonylamino-1-indanone; dapsone; solubilized chicken type II collagen; 15-deoxyspergualin; diacetyl-splenopentin; diaveridine; ditazol; droxicam; (Z)-3-[4-(acetyloxy)-5-ethyl-3-methoxy-1-naphthalenyl]-2-methyl-2-propenoic acid; ebselen; 1-p-chloro-benzyl-2-dimethyl-amino-methylcyclohexen-1,2; etoclofene; felbinac; fenclorac; fenclozic acid; fendosal; isoxepac; leflunomide; lobenzarit; lonazolac-Ca; 5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-3-(dimethylamino)-4-thiazolidinone; 5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-3-(methylamino)-4-thiazolidinone; bumadizon-calcium; azapropazone; D-myoinositol-1.2.6-trisphosphate; ibufenac; nimesulide; oxamethacin; oxaprozin; suxibuzone; pirprofen; proquazone; triamcinolone acetonide; suprofen; tenoxicam; tiaprofenic acid; tolfenamic acid; difenpyramide; isofezolac; tiopronin; 5-thiopyridoxine; hydrocortisone, as well as pharmaceutically acceptable ester and salt derivatives thereof; prednisolone, as well as pharmaceutically acceptable ester and salt deriva-

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tives thereof; cortisone, as well as pharmaceutically acceptable ester and salt derivatives thereof; triamcinolone, as well as pharmaceutically acceptable ester and ether derivatives thereof; betamethasone, as well as pharmaceutically acceptable ester and salt derivatives thereof; aspirin; calcium acetylsalicylate; choline salicylate; choline magnesium trisalicylate; magnesium salicylate; salsalate; N,N'-diphenyl-p-phenylenediamine; tenidap; 1-isobutyl-3,4-diphenylpyrazole-5-acetic acid and carprofen.

37. The composition of Claim 16 for treating anklosing spondylitis wherein the medicament is selected from the group consisting of: isoxicam; ketoprofen; diclofenac; fenclofenac; phenylbutazone; prenazone; nabumetone; indomethacin; sulindac; carprofen; dexamethasone, as well as pharmaceutically acceptable ester and salt derivatives thereof; proquazone; ibuprofen; tenoxicam; piroxicam; tiaprofenic acid; tolfenamic acid; pirofen; hydrocortisone, as well as pharmaceutically acceptable ester and salt derivatives thereof; prednisolone, as well as pharmaceutically acceptable ester and salt derivatives thereof; cortisone, as well as pharmaceutically acceptable ester and salt derivatives thereof; prednisone, as well as pharmaceutically acceptable ester derivatives thereof; methylprednisolone, as well as pharmaceutically acceptable ester and salt derivatives thereof; triamcinolone, as well as pharmaceutically acceptable ester and ether derivatives thereof; betamethasone, as well as pharmaceutically acceptable ester and salt derivatives thereof; aspirin; calcium acetylsalicylate; choline salicylate; choline magnesium trisalicylate; magnesium salicylate; salsalate; imidazole 2-hydroxybenzoate; diflunisal; sulfasalazine; benorylate; naproxen; and oxyphenbutazone.

38. The composition of claim 16 for treating osteoarthritis wherein the medicament selected from the group consisting of prednisone, as well as pharmaceutically acceptable ester derivatives thereof; nabumetone; ketoprofen; phenylbutazone; the (S)(+) enantiomer of carprofen; dexamethasone, as well as pharmaceutically acceptable ester and salt derivatives thereof; diclofenac; diflunisal; diphenpyramide; fenbufen; oxyphenbutazone; indomethacin; glucametacin; isoxicam; lonazolac-Ca; S-adenosylmethionine; bumadizon-calcium; diacetylrhein;

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proquazone; naproxen; nimesulide; oxamethacin; pirprofen; prenazone; sulindac; suprofen; tenoxicam; tiaprofenic acid; hydrocortisone, as well as pharmaceutically acceptable ester and salt derivatives thereof; prednisolone, as well as pharmaceutically acceptable ester and salt derivatives thereof; cortisone, as well as pharmaceutically acceptable ester and salt derivatives thereof; methylprednisolone, as well as pharmaceutically acceptable ester and salt derivatives thereof; triamcinolone, as well as pharmaceutically acceptable ester and ether derivatives thereof; betamethasone, as well as pharmaceutically acceptable ester and salt derivatives thereof; aspirin; calcium acetylsalicylate; choline salicylate; choline magnesium trisalicylate; magnesium salicylate; salsalate; and etodolac.

39. The composition of claim 16 for treating tendinitis or tenosynovitis wherein the medicament is selected from the group consisting of: the (S)(+) enantiomer of carprofen; dexamethasone, as well as pharmaceutically acceptable ester and salt derivatives thereof; diclofenac; fenbufen; nimesulide; oxamethacin; pirprofen; proquazone; sulindac; tenoxicam; tiaprofenic acid; hydrocortisone, as well as pharmaceutically acceptable ester and salt derivatives thereof; prednisolone, as well as pharmaceutically acceptable ester and salt derivatives thereof; cortisone, as well as pharmaceutically acceptable ester and salt derivatives thereof; prednisone, as well as pharmaceutically acceptable ester derivatives thereof; methylprednisolone, as well as pharmaceutically acceptable ester and salt derivatives thereof; triamcinolone, as well as pharmaceutically acceptable ester and ether derivatives thereof; betamethasone, as well as pharmaceutically acceptable ester and salt derivatives thereof; indomethacin; aspirin; pyridoxine; pyridoxal; pyridoxal 5-phosphate; and pyridoxamine.

40. The composition of Claim 16 for treating carpal tunnel syndrome and other cumulative trauma disorders wherein the medicament is selected from the group consisting of: diclofenac; dexamethasone acetate; methylprednisolone acetate; hydrocortisone acetate; pyridoxine; pyridoxal; pyridoxal 5-phosphate; and pyridoxamine.

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41. The composition of Claim 16 for treating chronic discoid or systemic lupus erythematosus wherein the medicament is selected from the group consisting of: hydroxychloroquine; quinacrine; chloroquine; amodiaquine; triquine composition; 15-deoxyspergualin; dexamethasone, as well as pharmaceutically acceptable ester and salt derivatives thereof; leflunomide; cyclosporins A through I; methylprednisolone, as well as pharmaceutically acceptable ester and salt derivatives thereof; eicosapentaenoic acid; hydrocortisone, as well as pharmaceutically acceptable ester and salt derivatives thereof; prednisolone, as well as pharmaceutically acceptable ester and salt derivatives thereof; cortisone, as well as pharmaceutically acceptable ester and salt derivatives thereof; prednisone, as well as pharmaceutically acceptable ester derivatives thereof; triamcinolone, as well as pharmaceutically acceptable ester and ether derivatives thereof; triamcinolone acetonide; fluocinolone acetonide; fluocinonide; flurandrenolide; betamethasone valerate; betamethasone 17,21-dipropionate; aspirin; azathioprine; and cyclophosphamide.

42. The composition of Claim 16 for treating pneumoconiosis due to inhalation of asbestos particles, inhalation of stone dust or quartz or inhalation of other causative agents such as graphite, coal dust, particles produced by metal grinding, talc or corn dust wherein the medicament is selected from the group consisting of: D-penicillamine; 4H-4-phenylthieno-[3,2-c]-[1]-benzopyran-2-carboxylic acid; 4H-2-carboxamido-4-phenylthieno-[3,2-c]-[1]-benzopyran; N-acetylcysteine; dexamethasone; indomethacin; prednisolone, as well as pharmaceutically acceptable ester and salt derivatives thereof; hydrocortisone, as well as pharmaceutically acceptable ester and salt derivatives thereof; flurbiprofen; and S-carboxymethylcysteine.

43. The composition of Claim 16 for treating chronic obstructive pulmonary disease wherein the medicament is selected from the group consisting of: D-penicillamine; 4H-4-phenylthieno-[3,2-c][1]-benzopyran-2-carboxylic acid; 4H-2-carboxamido-4-phenylthieno-[3,2-c][1]benzopyran; N-acetylcysteine; dexamethasone, as well as pharmaceutically acceptable ester and salt derivatives thereof; indomethacin; prednisolone, as well

as pharmaceutically acceptable ester and salt derivatives thereof; hydrocortisone, as well as pharmaceutically acceptable ester and salt derivatives thereof; flurbiprofen; S-carboxy-methylcysteine; prednisone; and methylprednisolone, as well as pharmaceutically acceptable ester and salt derivatives thereof.

44. The composition of Claim 16 for treating inflammatory myopathies wherein the medicament is selected from the group consisting of: prednisone; methotrexate; cyclophosphamide; chlorambucil; azathioprine; and diazepam.

45. The composition of Claim 16 for treating inflammatory neuropathies wherein the medicament is selected from the group consisting of: cortisone, as well as pharmaceutically acceptable ester and salt derivatives thereof; prednisone, as well as pharmaceutically acceptable ester derivatives thereof; methylprednisolone, as well as pharmaceutically acceptable ester and salt derivatives thereof; triamcinolone, as well as pharmaceutically acceptable ester and ether derivatives thereof; betamethasone, as well as pharmaceutically acceptable ester and salt derivatives thereof; dexamethasone, as well as pharmaceutically acceptable ester and salt derivatives thereof; hydrocortisone, as well as pharmaceutically acceptable ester and salt derivatives thereof; prednisolone, as well as pharmaceutically acceptable ester and salt derivatives thereof; and ebselen.

46. The composition of Claim 16 for treating epilepsy wherein the medicament is selected from the group consisting of: dizocilpine; phenytoin; phenytoin-polyvinylpyrrolidone coprecipitate; phenytoin in combination with phenobarbital; phenobarbital; primidone; carbamazepine; ethosuximide; clonazepam; valproic acid; divalproex sodium; acetazolamide; acetazolamide sodium; prednisone; corticotropin; diazepam; lorazepam; felbamate; zonisamide; gabapentin; lamotrigine; and vigabatrin.

47. The composition of Claim 16 for treating Alzheimer's disease wherein the medicament is selected from the group consisting of: vasodilator or other nootropic direct brain metabolic enhancer co-agents including idebenone, propentophylline, pentoxifylline, citicoline, ebiratide, exifone,

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flunarizine, nimodipine, nicergoline, razobazam, rolipram, sabeluzole, phosphatidylserine, vinpocetine, ergoloid mesylates, bromvincamine, cyclandelate, isoxsuprene, naf-ronyl, papaverine, suloctidil, vinburnine, vincamine, vindeburnol, naloxone, ethyl 5-isopropoxy-4-methyl- β -carboline-3-carboxylate, *N'*-methyl- β -carboline-3-carboxamide, methyl 6,7-dimethoxy-4-ethyl- β -carboline-3-carboxylate, ethyl 5-methoxy-4-ethyl- β -carboline-3-carboxylate, ifenprodil, piracetam, aniracetam, pyroglutamic acid, tenilsetam, pramiracetam, oxiracetam, rolziracetam, etiracetam and dupracetam; neurotransmission enhancer co-agents including amantadine, calcium hopantenate, lisuride, and indeloxazine; ifenprodil; tiapride; psychotherapeutic co-agents including haloperidol, bromperidol, thioridazine, thiothixene, fluphen-azine, perphenazine optionally with amitriptyline, and molindone; acetylcholinesterase inhibitors including physostigmine optionally with phosphatidylcholine, heptyl-physostigmine, tacrine optionally with phosphatidylcholine, (*)-9-amino-1,2,3,4-tetrahydroacridin-1-ol optionally with phosphatidylcholine, metrifonate, velnacrine, methanesulfonyl fluoride, phenylmethylsulfonyl fluoride, huperzine A, huper-zine B, edrophonium, miotine and galanthamine; calcium channel blocker co-agents including diltiazem, verapamil, nifedipine, nicardipine, isradipine, amlodipine and felodipine; biogenic amines and co-agents related thereto including clonidine, guanfacine, alaproclate, fipexide, zimeldine and citalopram; antirage co-agents including propranolol, carbamazepine and fluoxetine; benzodiazepine tranquilizers including diazepam, prazepam, chlordiazepoxide optionally with clidinium or amitriptyline or esterified estrogen, oxazepam and clorazepate dipotassium; angiotensin converting enzyme inhibitors includ-ing captopril optionally with hydrochlorothiazide, enalapril optionally with hydrochlorothiazide, enalaprilat, fosinopril, lisinopril, ramipril, epicaptopril, alacepril, quinapril, perindopril, delapril, cilazapril, pivalopril, rentiapril, zofenopril and zofenoprilat; co-agents which may enhance acetylcholine synthesis, storage or release including phos-phatidylcholine, 4-aminopyridine, 3,4-diaminopyridine, choline, vesamicol, tetra-phenylurea, nicotinamide, secoverine

and bifemelane; acetylcholine postsynaptic receptor agonists including arecoline, oxotremorine, bethanechol, ethyl nipecotate and levacecarnine; ganglioside GM₁; mixed cow brain gangliosides; specific monoamine oxidase-A inhibitors including moclobemide; *N*-methyl-D-aspartate glutamate receptor antagonists including milacemide, trihexyphenidyl, ethopropazine, procyclidine, diphenhydramine, dizocilpine, amantadine and memantine; nonsteroidal anti-inflammatory co-agents including naproxen, flurbiprofen, aspirin, mesalamine, phenylbutazone, sulindac, oxaprozin, D-penicillamine, salsalate, diflunisal, piroxicam, indomethacin, etodolac, meclofenamate, ibuprofen, fenoprofen, ketoprofen, mefenamic acid, nabumetone, auranofin, tolmetin, ketorolac tromethamine, diclofenac and deferoxamine; (-)deprenyl; thiamine; thiamine disulfide *O,O*-diisobutyrate; anfacine; antioxidant co-agents which may be used in combination including ascorbic acid, α -tocopherol, *N*-acetylcysteine, β -carotene, D-penicillamine, cysteamine, ebselen and deferoxamine; specific monoamine oxidase-B inhibitors including lazabemide; linopirdine; D-cycloserine; serotonergic receptor antagonists including ketanserin and mianserin; and estrogen.

48. The composition of Claim 16 for treating myasthenia gravis wherein the medicament is selected from the group consisting of: prednisone; azathioprine; pyridostigmine; neostigmine; atropine; propantheline; and ephedrine and derivatives thereof.

49. The composition of Claim 16 for treating multiple sclerosis wherein the medicament is selected from the group consisting of: 15-deoxyspergualin; leflunomide; methylprednisolone, as well as pharmaceutically acceptable ester and salt derivatives thereof; prednisone, as well as pharmaceutically acceptable ester derivatives thereof; dexamethasone; corticotropin; cyclosporins A through I; amantadine; diazepam; clonazepam; baclofen; carbamazepine; phenytoin; isoniazid; primidone; propranolol; amitriptyline; oxybutynin chloride; propantheline bromide; imipramine; carbachol; bethanechol chloride; phenoxybenzamine; tizanidine; chlorpromazine; diacetylrhein; alfa-2a interferon; alfa-2b interferon; alfa-N3 interferon; beta interferon; gamma-1b interferon; copolymer-1;

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4-aminopyridine; 3,4-diaminopyridine; cyclophosphamide; prednisolone, as well as pharmaceutically acceptable ester and salt derivatives thereof; triamcinolone, as well as pharmaceutically acceptable ester and ether derivatives thereof; azathioprine; and bovine myelin.

50. The composition of Claim 16 for treating inflammatory site edema wherein the medicament is selected from the group consisting of: cyproheptadine; clemastine; setastine; indomethacin; piroxicam; phenylbutazone; dexamethasone, as well as pharmaceutically acceptable ester and salt derivatives thereof; phenidone; nordihydroguaiaretic acid; ketoconazole; suprofen; ketoprofen; indoprofen; sudoxicam; naproxen; meclofenamic acid; ibuprofen; diclofenac; fenoprofen; hydroxychloroquine; 2,6-diamino-N-([1-(1-oxotridecyl)-2-piperidinyl]methyl)-hexanamide; bucloxic acid; butibufen; carprofen; the (S)(+) enantiomer of carprofen; 6-(2,4-difluorophenoxy)-5-methylsulfonylamino-1-indanone; loxoprofen; diaveridine; ditazol; droxicam; (Z)-3-[4-(acetyloxy)-5-ethyl-3-methoxy-1-naphthalenyl]-2-methyl-2-propenoic acid; ebselen; 1-p-chlorobenzyl-2-dimethyl-aminomethylcyclohexen-1,2; etoclofene; flufenamic acid; benzydamine; mefenamic acid; fenbufen; felbinac; fenclorac; fenclozic acid; fendosal; isoxepac; imidazole salicylate; isoxicam; tolmetin; leflunomide; isofezolac; 1-isobutyl-3,4-diphenylpyrazole-5-acetic acid; S-adenosylmethionine; D-myoinositol-1.2.6-trisphosphate; diacetylrhein; cinmetacin; tinoridine; nimesulide; prenazone; naphthypramide; proquazone; ketorolac; hydrocortisone, as well as pharmaceutically acceptable ester and salt derivatives thereof; prednisolone, as well as pharmaceutically acceptable ester and salt derivatives thereof; cortisone, as well as pharmaceutically acceptable ester and salt derivatives thereof; prednisone, as well as pharmaceutically acceptable ester derivatives thereof; methylprednisolone, as well as pharmaceutically acceptable ester and salt derivatives thereof; triamcinolone, as well as pharmaceutically acceptable ester and ether derivatives thereof; betamethasone, as well as pharmaceutically acceptable ester and salt derivatives thereof; and N,N'-diphenyl-p-phenylenediamine.

51. The composition of Claim 16 for treating post-event acute

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central nervous system trauma, including stroke and spinal cord trauma wherein the medicament is selected from the group consisting of: heparin calcium; heparin sodium; warfarin; ticlopidine; aminophylline; isoproterenol; methohexital sodium; tirilazad mesylate; derivative of tirilazad in which the steroid portion of the chemical structure has been replaced with the tetramethyl chroman portion of d- α tocopherol; allopurinol; ebselen; methylprednisolone; aspirin; sulfipyrazone; dipyridamole; clofibrate; tissue plasminogen activator; streptokinase; trihexyphenidyl; ethopropazine; procyclidine; diphenhydramine; dizocilpine; amantadine; memantine; milacemide; dextrorphan; moclobemide; and low molecular weight sulphate/dermatan sulphate glycoaminoglycan heparinoid mixtures.

52. The composition of Claim 16 for treating post-event consequences of kidney ischemia and reperfusion wherein the medicament is selected from the group consisting of: trimetazidine; allopurinol; bucloxic acid; indometacin; ebselen; methylprednisolone; prednisone; cyclophosphamide; chlorambucil; cyclosporins A through I; azathioprine; and N,N'-diphenyl-p-phenylenediamine.

53. The composition of Claim 16 for treating myocardial infarction wherein the medicament is selected from the group consisting of: trimetazidine; allopurinol; lidocaine; procainamide; acebutolol; alprenolol; atenolol; betaxolol; carteolol; esmolol; labetalol; metoprolol; nadolol; oxprenolol; penbutolol; pindolol; propranolol; sotalol; timolol; sustained-release trinitroglycerin; sodium nitroprusside; isosorbide 5-mononitrate; isosorbide dinitrate; diltiazem; verapamil; nifedipine; nicardipine; isradipine; amlodipine; felodipine; N,N'-dimethylthiourea; N-2-mercaptopropionylglycine; deferroxamine; ebselen; taurine; streptokinase; urokinase; acylated streptokinase-plasmin complex; recombinant tissue plasminogen activator; heparin; aspirin; captopril; enalapril; fosinopril; lisinopril; ramipril; quinapril; quinapril/hydrochlorothiazide combinations; benazepril; and clofibrate.

54. The composition of Claim 16 for treating an inflammatory disease comprising the method of Claim 1 and additionally

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administering a medicament previously recognized as having general anti-inflammatory properties and, preferably, as having usefulness in clinically treating chronic inflammatory diseases of varying origin, said previously recognized agent wherein the medicament is selected from the group consisting of: tilomisolet; tenidap; 1-[(4-chlorophenyl)methyl]-2-methyl-5-(quinolinylmethoxy)-1H-indole-3-acetic acid; tepoxalin; scalaradial; neutral macrolide of molecular formula $C_{44}H_{69}NO_{12} \cdot H_2O$ derived from Streptomyces tsukubaensis No. 9993; tirilazad mesylate; derivative of tirilazad in which the steroid portion of the chemical structure has been replaced with the tetramethyl chroman portion of d- α tocopherol; pentoxifylline; indoxole; bimetopyrol; flumizole; phenidone; N,N'-diphenyl-p-phenylenediamine; ebselen; bucolome; sodium 2-[4-(2-oxocyclopentylmethyl)phenyl]propionate dihydrate; sideritoflavone; cirsiolol; hypolaetin-8-glucoside; hypolaetin; oroxindin; quercetagetin-7-glucoside; gossypin; hibifolin; gossypetin; leucocyanidol; indoprofen; crude extract of Mandevilla velutina; 1-[3-(naphth-2-ylmethoxy)phenyl]-1-(thiazol-2-yl)propyl methyl ether; epirizole; DL-2-(4-hexyloxyphenyl)-glycine octyl ester; DL-2-[4-(5,5-dimethyl-hexyloxy)phenyl]-glycine octyl ester; meloxicam; kojic acid; 2-(2-hydroxy-4-methylphenyl)aminothiazole hydrochloride; 2-(p-bromo-phenyl)-9-dimethylaminopropyl-9H-imidazo[1,2-a]benzimidazole; benoxaprofen; flunoxaprofen; emorfazone; misoprostol; 6-methoxy-2-naphthylacetic acid; niflumic acid; clidanac; perisoxal; proglumetacin; 4-(2-chlorophenyl)-2-[2-(4-isobutylphenyl)-ethyl]-6,9-dimethyl-6H-thieno[3,2-f][1,2,4]triazolo-[4,3a][1,4]diazepine; paramethasone; paramethasone 21-acetate; and paramethasone disodium phosphate.

55. The composition of claim 23 wherein the nonabsorbable primary amine polymer having at least one free primary amine group is selected from the group consisting of

- a. naturally occurring polysaccharides having β -1,2, β -1,3, β -1,4 and/or β -1,6 linkages containing aminosugars including the chitin class of biopolymers having the general structure of poly- β -(1 \rightarrow 4)-N-acetyl-D-glucosamine, and bearing at least one free primary amine group;
- b. deacetylated naturally occurring polysaccharides, having

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at least one N-acetylated residue, wherein upon chemical deacetylation thereof, said deacetylated naturally occurring polysaccharide is a high molecular weight derivative bearing primary amine groups directly linked to sugar carbons; including chitosan but not limited to chitosan;

c. chemically aminated polysaccharides from the group consisting of:

aminodeoxy polysaccharides such as 2-amino-2-deoxy-cellulose; aminoalkyl-, amino(hydroxyalkyl)-, aminoalkyl-ether-, and amino(hydroxyalkyl)-ether- derivatives of cellulose, chitin and other naturally occurring non-digestible carbohydrates selected from the group consisting of

$H_2N-(CH_2)_n-[carbohydrate]$ where $n = 1-10$, including alkyl isomers;

$H_2N-(CH_2)_m-CHOH-(CH_2)_n-[carbohydrate]$, where $m = 0-10$ and $n = 0-10$;

$H_2N-(CH_2)_n-O-[carbohydrate]$ where $n = 1-10$;

$H_2N-(CH_2)_m-CHOH-(CH_2)_n-O-[carbohydrate]$ where $m = 0-10$ and $n = 0-10$;

aminobenzyl- derivatives of cellulose, chitin or other naturally occurring non-digestible carbohydrates selected from the group consisting of

$H_2N-C_6H_4-(CH_2)_n-[carbohydrate]$,

$H_2N-CH_2-C_6H_4-(CH_2)_n-[carbohydrate]$,

$H_2N-C_6H_4-(CH_2)_n-O-[carbohydrate]$ where $n = 0 - 10$, and

$H_2N-C_6H_4-(CH_2)_m-CHOH-(CH_2)_n-O-[carbohydrate]$ where $m = 0-10$ and $n = 0-10$, including p-, o- and m-benzene ring amino-isomers, aminomethyl- isomers and alkyl group isomers thereof;

guanidine and aminoguanidine derivatives of cellulose, chitin or other naturally occurring non-absorbable carbohydrates selected from the group consisting of:

$H_2N-C(=NH)-[carbohydrate]$;

$H_2N-C(=NH)-(CH_2)_n-[carbohydrate]$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$H_2N-C(=NH)-O-(CH_2)_n-[carbohydrate]$, where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

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$H_2N-C(=NH)-NH-[carbohydrate]$;

$H_2N-C(=NH)-NH-(CH_2)_n-[carbohydrate]$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$H_2N-C(=NH)-NH-(CH_2)_n-O-[carbohydrate]$, where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$H_2N-C(=NH)-N=CH-(CH_2)_n-[carbohydrate]$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$H_2N-C(=NH)-N=CH-(CH_2)_n-O-[carbohydrate]$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$H_2N-NHC(=NH)-NH-[carbohydrate]$;

$H_2N-NHC(=NH)-NH-(CH_2)_n-[carbohydrate]$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$H_2N-NHC(=NH)-NH-(CH_2)_n-O-[carbohydrate]$, where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$H_2N-NHC(=NH)-N=CH-(CH_2)_n-[carbohydrate]$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$H_2N-NHC(=NH)-N=CH-(CH_2)_n-O-[carbohydrate]$, where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$H_2N-C(=NH)-NH-NH-[carbohydrate]$;

$H_2N-C(=NH)-NH-NH-(CH_2)_n-[carbohydrate]$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$H_2N-C(=NH)-NH-NH-(CH_2)_n-O-[carbohydrate]$, where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$H_2N-C(=NH)-NH-N=CH-(CH_2)_n-[carbohydrate]$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$H_2N-C(=NH)-NH-N=CH-(CH_2)_n-O-[carbohydrate]$, where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

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d. primary amine, aminoguanidine and guanidine derivatives of sucrose polyesters having one or more carbonyl trapping functional group per molecule wherein each carbonyl trapping functional group is in the ω -, ω -1 or other isomeric position within the fatty acyl chains, wherein each fatty acyl chain may have from 3 to 26 carbons, from one to five nitrogen functional groups and from one to 24 hydroxyl groups;

e. synthetic polysaccharides consisting partly or entirely of aminosugars bound by β -1,2, β -1,3, β -1,4 and/or β -1,6 linkages;

f. mixed polysaccharide polymeric derivatives wherein primary amine, aminoalkyl (one to ten carbons per alkyl group), amino-hydroxyalkyl (one to ten carbons per alkyl group and one to ten hydroxyl groups per alkyl group), aminoguanidine, aminoguanidinyl-alkyl (one to ten carbons per alkyl group), aminoalkylguanidinyl (one to ten carbons per alkyl group), guanidine, aminobenzene and/or aminoalkylbenzene (one to ten carbons per alkyl group) functional groups are covalently attached to matrices such as epi-chlorohydrin copolymers of cellulose or chitin and wherein hydrocarbon spacer groups may include alkene as well as alkyl groups; and

g. non-polysaccharide polymeric derivatives wherein primary amine, aminoalkyl (one to ten carbons per alkyl group), amino-hydroxyalkyl (one to ten carbons per alkyl group and one to ten hydroxyl groups per alkyl group), aminoguanidine, aminoguanidinyl-alkyl (one to ten carbons per alkyl group), aminoalkylguanidinyl (one to ten carbons per alkyl group), guanidine, aminobenzene and/or aminoalkylbenzene (one to ten carbons per alkyl group) functional groups are covalently attached to a synthetic non-digestible polymer selected from the group consisting of polystyrene, styrene-divinylbenzene copolymer, polyvinyl alcohol and crosslinked derivatives thereof, and wherein hydrocarbon spacer groups may include alkene as well as alkyl groups.

56. A composition of Claim 16 additionally containing an effective amount of an anti-oxidant.

57. A composition of Claim 36 additionally containing an effective amount of an anti-oxidant.

58. A composition of Claim 38 additionally containing an

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effective amount of an anti-oxidant.

59. A composition of Claim 39 additionally containing an effective amount of an anti-oxidant.

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/19, 31/195

US CL :514/568, 569, 570, 825, 885

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/568, 569, 570, 825, 885

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

MERCK INDEX

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	"PHYSICIANS' DESK REFERENCE", 45TH EDITION, published 1991 by Medical Economics Data (N.J.), page 1044, see page 1044.	1-5, 7-15 ----- 6, 16-59
X -- Y	US, A, 3,956,504 (SAWYER), 11 May 1976, see whole document.	1-15 ----- 16-59

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G*	document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means		
P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
01 AUGUST 1995	21 AUG 1995
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer FRANCISCO C. PRATS
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B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS, REGISTRY, CHEMICAL ABSTRACTS, EMBASE, BIOSIS, MEDLINE, WPIDS (WORLD PATENT INDEX)
search terms: para-aminobenzoic acid, inflamm?, anti-inflamm?, sulindac